FEMALE SPEAKER: Good morning, everyone. As you're joining, we're going to first have you hear from Dr. Gores.

GREGORY J. GORES: Thank you. I really want to welcome everybody to the Mayo Clinic COVID Live Webinar Series. I'm Greg Gores, I'm the executive dean for research at the Mayo Clinic. We have three outstanding panelists with us this morning.

We have Dr. Andrew Badley, he's professor of medicine in molecular medicine, chair of molecular medicine, and chair of the Mayo Clinic COVID-19 Task Force, and consultant in infectious diseases. We have Dr. Michael Joyner, who is professor of anesthesia, a principal investigator of the Expanded Access Program using convalescent plasma to fight COVID illness. And Dr. Elie Berbari, who is professor of medicine, chair of infectious diseases at Mayo Clinic Rochester, and chair of the Mayo Clinic COVID-19 Diagnostic and Stewardship Task Force.

Probably, never before had such a bright light been shown on the science of emerging pathogen in our lifetimes, and we have three outstanding people to highlight what the current state of knowledge is. After each person speaks, then we will go through a number of questions that people have sent in, and address these questions in an organized fashion.

So we will start with Dr. Berbari, who will be talking about testing, pathogenesis, and testing of COVID-19. So welcome, Dr. Berbari.

ELIE R. BERBARI: Thank you, Greg. And I have few slides to present. I want to thank all the attendees for joining this morning on this special webinar. All right. So just to put things into perspective, the coronavirus so far, as of this morning, we have more than 4.8 million individuals that have been infected, and the pandemic has claimed the lives of more than 318,000 individuals.

The SARS-CoV-2, the virus responsible for the COVID-19, can be transmitted in a variety of ways from an infected individual to a susceptible individuals. One of the most important ways is through droplet transmission, but also, through either direct or indirect contact. Another way that the virus can be transmitted is through droplet nuclei that are airborne, and can be suspended in the air for an extended period of time. In a health care setting, those droplet nuclei can be generated through aerosol-producing procedures that may involve the airways.

Human coronaviruses have been known for a long time as a cause of cold. And here is a short list of some of those coronaviruses that can be picked up on respiratory pathogen panels that have pre-existed the COVID-19 pandemic. But it also can cause severe disease. Over the last 20 years, we've identified three different viruses that are associated with severe disease: SARS 2002-2003, MERS 2012, and the most recent pandemic with SARS-CoV-2.

We have two major tests that are currently utilized in clinical practice to help in the diagnosis of COVID-19, the nucleic acid amplification test, and the antibody test. The PCR tests, or nucleic acid amplification test, help diagnose current infections with SARS-CoV-2; whereas antibody detection helps us with past exposure to SARS-CoV-2. And I'll elaborate a little bit more on each of these tests.

Indications for molecular testing as indicated was originally for symptomatic patients. But as we understood better the viral shedding patterns, we realized that there are many more patients who can shed the virus who are asymptomatic. At the Mayo Clinic, many of patients who are asymptomatic are tested in the setting of pre-surgical or pre-procedural practice, or prior to initiation of immunosuppressive therapy. Other indications for asymptomatic testing is around possible high-risk exposures or in high-risk settings, such as nursing homes and hospitals.

The molecular testing is performed on a nasopharyngeal swab, which is the preferred method of collecting a specimen. Other ways of collecting specimens that may be acceptable are oropharyngeal swab. As the disease advances in some patients from an upper respiratory disease to a lower pulmonary disease, specimens such as sputum, BAL, tracheal secretions may be utilized for molecular testing.

Perhaps the most striking difference of SARS-CoV-2 when compared to other coronaviruses is its ability to shed even before symptoms develop. In this slide, you can see the amount of viral shedding at the highest during the day or two before symptoms occur.

Antibody testing at Mayo has been utilized now since early April. It's not an alternative or additional marker of acute or recent infection. It focus on IgG-class, but there are many other assays that could detect IgM or other immunoglobulins such as IgA. The one that we use at Mayo is depicted on this slide, and it detects antibodies against the Spike protein.

This is some validation data that we utilized to validate the IgG test at Mayo, and it shows that the majority of patients who were symptomatic developed and IgG titer after 14 or 15 days of symptoms onset. This is to recap a little bit on the immunoglobulin or IgG testing, that the results suggest prior infection and protective immunity cannot be inferred. We are seeing a number of tests that are indeterminate. And these are likely false positive indeterminate, and do not reflect, most of the time, a lower titer.

I have one more or two more slides. One of the important parts of developing a Diagnostic Stewardship Program in a health care organization at Mayo is our ability to predict utilization in this fast-moving environment. And having the ability to develop these predictive analytical data is so crucial to be able to react and adjust our lab capacity with this growing need for PCR testing.

The other important part of a Diagnostic Stewardship Program is the ability to develop guidance and disseminate that guidance to health care workers in a large organization. At Mayo, we have a platform called the Ask Mayo Expert that was utilized for that purpose.

With that, I want to thank all members of our Diagnostic Stewardship Team that have played a significant role in helping our organization develop those testing, introduce those testing into the clinical practice very fast, communicate that information, and also wire those testing into our practice.

With that, I'll conclude my presentation. And thanks for listening.

GREGORY J. GORES: Well thank you so much, Dr. Berbari. Our next speaker will be Dr. Michael Joyner, who will review the Expanded Access Program using convalescent serum as therapy. So welcome, Dr. Joyner.

MICHAEL J. JOYNER: Thank you, Greg. So we'll just go to the next slide. We have a straightforward title here.

So the conceptual model is straightforward. We want to take a COVID patient who's recovered, draw blood from that patient, harvest neutralizing antibodies from the plasma or serum. And use this as therapy in individuals who are currently infected, which is what we're doing in the Expanded Access Program, or potentially develop techniques to use this in prophylaxis for either pre-exposure or post-exposure prophylaxis. So this is the conceptual model. Next slide.

This was used in 1918 during the flu epidemic. This is a sailor who was treated at the Portsmouth Naval Hospital several times with serum in this particular case, which is plasma without the clotting factors. You can see this individual was treated, and his fever went down, and he recovered. Next slide, please.

There was actually quite a bit of convalescent plasma used in 1918. And when you look at all the data that's out there, about 54 out of 336 young people treated in 1918 died, versus 452 out of 1,219 in this recent meta analysis, or 37% who have died. Historically, if you look at convalescent plasma prior to World War II for many, many indications, somewhere between a third or 60% of patients seem to improve. Next slide, please.

So the summary is simple. It's worked in the past, yes. There are many examples of prophylaxis. Probably, a number of people on this call or on this Zoom conference have received, for example, Ig shots for hepatitis A prophylaxis.

Early use seems better in a variety of settings. Certainly, there had been attempts in the current crisis to add rescue therapy. And typically, after we get past the convalescent plasma phase, concentrated products, hyperimmune globulins and gamma globulin shots emerge. Next slide, please.

So my awareness of this came in late February. There was a rising awareness, or a raising awareness at Mayo during March. There was an emergent network of individuals interested in this. We engaged the FDA starting in the middle of March. And with the FDA, developed an Expanded Access Program. There were also plenty of randomized trials going on, and I'll give you the results so far. Next slide.

So this is what happened in the end of February. Arturo Casadevall, who's a well-known expert in infectious disease, wrote an op-ed or commentary in the *Wall Street Journal* describing the use of convalescent plasma in the 1930s to stop a measles outbreak in a boy's school. Next slide.

Arturo's a close friend of mine, so I e-mailed him and said, we could do this at scale. This is just an example of the paper that he cited in that *Wall Street Journal* experience. Next slide.

So awareness was raised at Mayo in early March. The blood bank has done this before at the Mayo Clinic on a boutique basis for rare diseases. And they were completely on board, and said this could be done. Next slide.

By the middle of March, no one had said no. And no one said yes, so we pressed on. A network formed around Dr. Casadevall, which included investigators from a number of institutions. The Johns Hopkins groups, which is on prophylaxis in health care workers, and they had written a protocol, had FDA IND applications in, and so forth. I repurposed my lab, we identified a number of local experts, and started to think about a treatment trial. Next slide, please.

So we began to communicate with the FDA in the Center for Biologics. There, they developed an emergency IND program toward the end of March. They then contacted us about an Expanded Access Program on the 30th of March, only about a month after we first started talking about this. The FDA indicated they needed IRB approval, which I found interesting. Dr. Scott Wright at the Mayo IRB said, the Mayo IRB could serve in this role, and also be a national IRB through various reliance protocols. Next slide.

In late March, there were a couple of efforts nationally to use convalescent plasma. This is a documented case in Houston. And it's unclear whether it was first given at Houston Methodist or Mt. Sinai. The blood bankers started to mobilize nationally at the end of March. Next slide.

So on the 1st of April, the Mayo IRB approved the Expanded Access Program, served as a central IRB, and we developed concurrently a website for our compliance registration and case report forms, also a navigator function, and a number of other things. Many people on this call, or at least some, may be part of our network. We rolled it out on the 3rd of April. Next slide, please.

And this is what it looks like. Next slide. As of today, we have about 2,100 locations or sites in all 50 states, and Puerto Rico plus the Pacific Islands. Next slide. This was day zero or day one, depending on how the clock goes. This is day 24. Next slide. So many, many sites. Next slide, please.

So what have we learned so far? Is that the United States government and Mayo can move fast. There at first, was not enough plasma. There was a gap between demand and supply. That's mostly been solved now.

The early safety data, which I'm going to show you in a minute, suggests there is no major risk of plasma administration in these patients. There are some incredible anecdotes out there. We are currently building out an exposure or case control analysis.

There are some interesting data floating out in peer review, which I think will only increase enthusiasm for this therapy. And again, once this data is out in the preprint world, I believe that efficacy will be shown, and demand will be driven further. Next slide, please. So this is what we've seen in the first 5,000 patients. Next slide. And if you'll hit the Next button.

So we saw very, very low rates of transfusion-related acute lung injury. TACO and transfusion-related allergic reactions, much lower than we anticipated. It's very, very difficult to make a clear diagnosis of TRALI or TACO in patients in respiratory failure in the ICU.

Of the first 5,000 people we've studied, 2/3 were in the ICU. And of those ICU patients, about 18% had multi-organ failure or sepsis. So it was a very sick group, and again, making calls about TRALI and TACO is very difficult in this group. But the fact we did not see very large evidence or incidents of TACO and TRALI was reassuring to our Data Safety Monitoring Board, the Food and Drug Administration, and many people who are interested in using convalescent plasma. Next slide, please.

So as of May 15, about 11,000 patients had been treated in one month. I looked this morning, and we're up to 13,000 this morning. The infrastructure and compliance framework took seven to 10 days to develop before the first patient treatment.

I would think we would anticipate increased demand in the coming weeks and months. And demand will also increase because the people who make hyperimmune globulin need a source material. Demand might also increase if people begin to use this in a prophylactic way. Next slide, please.

Here is one case, and this is similar to many, many cases we hear about. This is from Dr. Bill Hartman at the University of Wisconsin. We had a relatively healthy 58-year-old guy on 60 liters of O2. Wanted to give him convalescent plasma, but he was confused and delirious. So his brother had power of attorney, and wanted to think about it. Had to intubate the guy, then the brother gave the OK. Transfused him, and he was extubated 24 hours later, and has been weaned down to room air.

But we won on this guy. There are many, many examples we get like this. We don't get too many emails or other contacts if this was a disaster. So we look forward to learning more as the case control and randomized clinical trials are done. Next slide, please. So we're optimistic, but we're not absolutely sure. Thank you very much.

GREGORY J. GORES: Thank you, Dr. Joyner. Our final panelist will be Dr. Andrew Badley, who'll be speaking a little bit about trials of pharmacologic agents. And also, what the horizon looks like for vaccines. So welcome, Dr Badley.

ANDREW D. BADLEY: Good morning, everyone. Thanks for taking the time to listen to us.

As Greg mentioned in the introduction, I was asked to oversee the COVID-19 Research Task Force at Mayo Clinic. And Mayo is very fortunate in that we have lots of experts across lots of domains.

So the way we've structured the Task Force was really as a platform. And now, we have 16 parallel work streams that we put together. And these work streams work on every individual protocol that comes through, and adds their level of value to synergize to create better individual research products.

So the domains where we have these work streams across the entire range of research that we could imagine. So it includes: basic virology, genetics research, reduction of environmental risk, community health research as to why different communities have different outcomes for the disease, pediatrics, artificial intelligence, and everything in between.

And so, we're very happy with the function of these work streams, and we believe that the quality of research that will be produced should be very good. And one of those work streams pertains to clinical trials and experimental therapeutics for COVID. Because there's no currently approved therapies for COVID, Mayo's position is that all therapies are experimental, and so should be subject to the scientific process.

There is a wide range of different therapies that are out there, and it is our goal to test a wide range of therapies across the spectrum of disease. And that spectrum of the disease includes prophylaxis, either pre or post-exposure prophylaxis, to outpatient therapy, to early inpatient therapy, all the way through to the critical care domain.

The kinds of therapies that we're evaluating at various stages includes small molecule inhibitors of the virus replication, antibody-based approaches which are intended to neutralize either the virus or the immune mediators, small molecules which inhibit immune signaling such as JAK inhibitors, and cell-based therapeutics. And a variety of those have been tried.

We're also interested in getting heavily involved in the vaccine space. Just a few comments about vaccines. So the goal of a vaccine is to in general, to take a viral protein, inject it into a human. That will drive an immune response, and hopefully, that immune response will be protective against infection.

We know for the history of vaccines for viruses, that some of those parts can occur but not necessarily all of those parts. So if you look at measles or polio, you can inject a viral protein, you'll develop an immune response, and that's virtually 100% protective.

Contrarily, if you take a vaccine against other viral diseases like hepatitis C or HIV, you can inject a viral protein, you can add your adjuvant of choice, you can get measurable immune response including antibodies, neutralizing antibody T-cell responses, but the degree of protection of those vaccines is zero.

And so what we don't know is that the SARS-CoV-2 space is, will it be preventable by a vaccine-based approach? And so, there is currently about 175 different vaccine candidates out there. Some of them are differentiated by the kind of protein and the kind of protein delivery system that's being used.

Some are differentiated by virtue of the adjuvants, which are molecules which can skew the immune response in one direction or the other. Some of them include T-cell adjuvants, and so we want to be very, very thoughtful about which of those vaccines we try and handle this here at Mayo.

There's also four different vaccine approaches that are being developed at Mayo. We've all heard in the news the past couple of days that the Moderna vaccine has generated a quantifiable immune response, which is a wonderful first step. And we look forward to getting into that game as well.

So with that, I'll end my comments, and pass it back to Greg now.

GREGORY J. GORES: OK. thank you, Dr Badley. So, we'll go forward with a question period. We've got several questions that we've solicited in the upcoming day, but also, some that are very live. And maybe, I'll handle the live questions first.

So Dr. Berbari, there have been reports of a virus antigen present in stool, and so there's this question of fecal-oral transmission. What's your take on that information? And has it impacted on how you handle patients going for colonoscopy, for example?

ELIE F. BERBARI: Thank you. I think with coronaviruses, there's evidence of transmission in the stool. This started with SARS in 2002-2003. And we do know that with COVID-19, there is a small proportion of patients who will have a GI illness.

So there's no doubt that the virus is present in the stool in a certain proportion of patients. The transmission is possible, and precautions should be made. It's not the main mode of transmission at this moment, but more information is needed.

GREGORY J. GORES: OK, thank you. And how about-- people want to know how long the virus is viable in the droplets or in fomites, these kind of activities. How does that influence your thinking about transmission?

ELIE F. BERBARI: Yeah. So let's talk a little bit about aerosol and aerosol-generating procedures. These are smaller particles that are in suspension in the air for a period of time, possibly one to two hours. In a health care setting, working with facilities and turnover of air is very important in controlling this possible mode of transmission.

And in terms of surface and how long does the virus live on surfaces? This has really been the subject of great debate, and they're many publications around it. It's probably there for a day or two. And environmental control is also part of COVID-19 prevention.

GREGORY J. GORES: Thank you. And I'm going to stay with you, Dr. Berbari. There's another question on sensitivity and specificity of anybody test. What do we know about that? And we may not have all of the data on sensitivity or specificity yet, but what are the emerging data?

ELIE F. BERBARI: Yeah. I think it's important to understand that what actually we're talking about, the IgG assay seems to be very sensitive in symptomatic patients. So if you test those patients two weeks after they had a PCR-confirmed illness, in many labs it seems to have a very high sensitivity. If you test them earlier or if you test asymptomatic patients, the sensitivity is lower.

In terms of other testing that might detect, IgA or IgM, there is a higher rate of false positivity with those tests. And those have to be interpreted in that light.

GREGORY J. GORES: OK. And in terms of some of the population-based studies, like the Santa Clara study, any comments on the specificity of the testing?

ELIE F. BERBARI: Again, I think if you're talking about population-based studies, there's still a little bit of unknown-- what's the background. And in the IgG assays, if you test samples from before COVID in 2018, none of those were IgG positive, at least in our hands.

GREGORY J. GORES: OK. Very interesting, thank you. Dr. Joyner, a lot of questions that you received in the past, I'm sure, about the dose response of the plasma antibody titers. Are you testing for neutralizing antibodies? Where do we stand with that input into this approach?

MICHAEL J. JOYNER: Yeah. Greg, that's a complicated question. The Expanded Access Program was started based on the idea that most, not all individuals who've recovered from CV-19 would generate antibodies. So there's no national or systematic approach to antibody titers in the units that are being transfused.

That various tremendously by blood banking system that acquires the units. So some blood banking systems, and there are about four or five major players in the US, are measuring antibodies. Others are not. Currently, the antibodies they are measuring are a non-specific look at IgG. Some of the labs are looking specifically in small subsets at neutralizing antibodies.

In the Expanded Access Program, we are developing a biobank in collaboration with the Vitalant Research Institute, which is one of the major blood bankers, to begin to obtain samples of plasma that were transfused to patients. And then, make those measurements in the plasma, and then try to relate those titers to outcomes.

So one of the things that'll be very interesting will be to take the 10% or perhaps 20% of people who have convalescent plasma with low or absent neutralizing antibodies, and almost use that plasma as a de facto placebo group as we look at a dose response curve.

So this is in process. We're collaborating with the FDA and Vitalant to set up our analysis plan. And with interested parties, to do the biobanking and statistics.

GREGORY J. GORES: OK. I'm going to stay with Dr Berbari. I'm going to stay with testing a little bit. There's been this issue of re-infection, of testing people over time. Your thoughts on that emerging data?

ELIE F. BERBARI: Yeah. I think early in the crisis and our understanding of the virus, there's been some unknown. And we found that many patients will have a positive PCR that would linger before two or three weeks after the onset of symptoms.

There is a body of emerging data that is now indicating that this is just that virus and that RNA, and not really a re-infection. This obviously needs more understanding. But at this moment, it seems like most patients that have lingering RNA when tested are asymptomatic, and this does not represent a live virus.

GREGORY J. GORES: OK. Dr. Badley, I'm going to go on to you. We're getting a lot of interest in therapy. But very topical, because the US President is actually on one of these drugs. People want to know what your take is on hydroxychloroquine in the context of COVID-19 illness?

ANDREW D. BADLEY: Yeah. So in vitro experiments indicate that hydroxychloroquine can reduce viral replication in a test tube. The presumed mechanism of action is altering the pH of the endolysosome which blocks the viral lifecycle. That has been used now in clinical cohort studies and in clinical trials.

There are multiple reports coming out showing that if there is a biologic effect, it is minimal. And there's multiple reports showing that there are QT and cardiac functions that can be impaired by them. So on balance, Mayo clinic is no longer using it as an off-label prescription option. We do have one clinical trial still ongoing in the high-risk exposed health care worker setting, but those patients have significant cardiac monitoring.

GREGORY J. GORES: OK, thank you. There are questions regarding people who are receiving anti-hypertensive therapy with renin, angiotensin, aldosterone therapies. And your thoughts on that? The drugs have been thought to increase of the receptor for COVID.

ANDREW D. BADLEY: So the dominant receptor for SARS-CoV-2 is the H2 receptor, as people are aware. That has led to questions about what modulates receptor expression.

It turns out that in a agnostic transcriptomic assessment, the tissues that express H2 receptors are the tissues where we see clinical correlates of viral infection. So that is, the oronasal pharynx, the lungs, the heart, the kidneys, and in fact the testes. Now there's reports about semen shedding of the-- oh, and the gut. There's now reports of semen shedding of the virus.

So there's also trials ongoing, and we, Mayo, is participating in one, about using ARBs to reduce the severity of infection. And those trials, as I said, are ongoing. There are questions about what can increase receptor expression, and there is some data to suggest that chronic ARB use up-regulates receptors. And the question is, does that enhance susceptibility to infection? To my knowledge, there is no data yet that that does enhance susceptibility to infection.

Other chronic cardiac conditions can also up-regulate H2 receptor expression. Colleagues here at Mayo have published a paper that hypertrophic obstructive cardiomyopathy, or HOCM, up-regulates H2 receptor expression within the heart. And so, it's possible that patients with chronic cardiac disease have enhanced susceptibility by virtue of that up-regulated receptor expression.

GREGORY J. GORES: Thank you. I'm going to stay with you, Dr. Badley. A common question is, people have a fever, do you take NSAIDS or Tylenol for this illness?

ANDREW D. BADLEY: Yes. So there were early reports that taking NSAIDs could exacerbate the immune profile and lead to worse outcomes. The subsequent reports have not validated that. In our hospitalized patients we have been using Tylenol, but I think it's fair to say there's no strong data to argue against NSAID use.

GREGORY J. GORES: OK. And then, what's your take on remdesivir?

ANDREW D. BADLEY: So remdesivir, as everyone knows now, has an emergency use authorization. That is based upon reduced length of hospital stay, and reduced severity illness of patients in hospital.

That raw data, which is from an NIAID has not yet been published. So we as a community have not been able to interrogate that data. The Gilead trials, two of them have stopped, two more will be stopping soon. And I anticipate that the data sets from those four trials will be attempted to be published in the very near future. So I think we'll see results.

Clinically, we find it to be safe and well-tolerated. And so, we anxiously await the data, but I think there is cause for cautious optimism.

GREGORY J. GORES: Thank you. I'm going to stay with you, Dr. Badley. That's a lot of questions about vitamin D, vitamin C as disease-modulatory agents.

ANDREW D. BADLEY: Yes. So the list of possible disease-modulatory agents is huge, and have led to a large number of clinical trials. My take on this data, and it hasn't changed recently, is that all of these are currently at the association stage. So the most recent one was the vitamin D data, where low vitamin D levels was associated with worse clinical outcome of disease. That has led to proposed clinical trials of vitamin D supplementation for patients who are infected.

It's very appropriate to assess the benefits, potential benefits, in a clinical trial setting. But to me, it an association not causation. And on a biological basis, I can certainly believe that low levels of vitamin D for example, might impair immune responsiveness. But if that's the premise, then I think altering vitamin D levels in the post-infectious setting is unlikely to make an impact on disease. But that's my opinion.

GREGORY J. GORES: OK. A question for Dr. Joyner. The question is, how many doses of the plasma can you receive, can it be repeated? And then the second one is, does it have an immunomodulatory effect, independent of perhaps antibodies neutralizing the virus?

MICHAEL J. JOYNER: So a couple of questions, there. When we started the Expanded Access Program, we restricted people to essentially one to two units within basically a nursing shift, eight to 12 hours. In lieu of the safety data and requests from others out in the network, we worked with the FDA, we have an IRB modification to permit individuals to give additional units of convalescent plasma.

There's a lot of concern out there in this literature about what's so-called antibody-dependent enhancement. We're working closely with Dr. Casadevall at Hopkins, who's the world's leading expert on that, as we review our data sets.

And at least so far in the first 5,000 people treated, we don't see a lot of evidence for, or any evidence for antibody dependent enhancement. But that is certainly a potential concern that is out there, and we continue to monitor our data sets for it.

GREGORY J. GORES: OK, thank you. Dr. Berbari, a little bit about transmission in pregnant women across the placenta, what the emerging data are, how we're guiding pregnant women to be thinking about this concern?

ELIE F. BERBARI: Yeah. There is some data around that, although this is still emerging. It does not seem that the virus is transmitted through the placenta. We're putting together a meta analysis on this right now.

And this is a particular group that may be at increased risk, pregnant women. But at least at this moment, transmission has not been documented. There might be adverse effect on the fetus and premature labor with COVID disease in pregnant women.

GREGORY J. GORES: OK, thank you. Dr. Badley, there's been a lot of questions on anti-coagulation, anti-platelet therapy with aspirin, as the disease has been reported to produce thromboembolic phenomenons, strokes, myocardial infarction, clots, unusual vasculitis in peripheral tissues, such as the toes. So your thoughts on aspirin, to begin with.

ANDREW D. BADLEY: Well, so there's no question that COVID disease is associated with a hypercoagulable state. We at Mayo have seen D-dimers as high as 100,000. On calls with other centers, I'm aware of patients who had clots in both upper extremities, both lower extremities, brain, and lungs at the same time, so it's a major sequelae.

There are trials out there comparing different coagulation approaches. We at Mayo are not doing one yet, but we may be doing one soon. When we see D-dimers in the mid-10,000 range, so around 50,000 or so, we often will ask our hematology colleagues to come by and advise on anti-coagulation approaches.

So I guess my summary is, yes, I think anti-coagulation is important. I think it's more complex than just picking one drug and blanketly using it because of the complications and co-morbidities in the patients who make it to the unit. And in our experience, the overwhelming majority of patients who make it to the unit have significant co-morbidities.

GREGORY J. GORES: Thank you. Dr Berbari, I want to go back to the pregnancy issue. Some of the questions regarding, is there a risk to the neonate, does breastfeeding provide immunity through immunoglobulins present in the breast milk? Can you guide our highly-informed audience in regards to those questions?

ELIE F. BERBARI: Yeah, I really don't have more to add. And maybe the panelists, Andrew or Mike, would have any additional information on this. I think this is a group that seems to be at higher risk. The transmission to the fetus is not documented. In terms of, there is some-- we don't understand if immunoglobulin or IgG confer immunity to be able to answer that at this moment. But maybe, Mike or Andrew could add to that?

ANDREW D. BADLEY: Totally agree with everything you said. One additive comment, is because the drugs that are used to treat COVID disease are all experimental, if you have a pregnant mother that has delivered and is on experimental therapies, FDA recommends not breastfeeding because we don't know the potential effects of the drugs in the breast milk.

GREGORY J. GORES: Mike?

MICHAEL J. JOYNER: The one thing I've learned as I've gone through with this is the interest in our friends in the immunoglobulin space and IgA, because IgA is secreted into the respiratory system and in respiratory tract, and how that may or may not be protective. And also, the fact that there may be things other than Ig in the circulating plasma that are protective. So it influences cellular immunity and so forth. So I do think that as important as neutralizing antibodies and Ig will be, there maybe more to the story than just Ig.

GREGORY J. GORES: OK. Thank you. A lot of questions, Doctor Badley, on young people, the nature of the illness in people, maybe under 30. And then, I will group some of these questions. Is there cross-immunity with the required vaccinations? Is there a relationship between the immunity of HLA status? And what about cross-immunity with other viruses in this family?

ANDREW D. BADLEY: Right. So yes, you did lump together a lot of questions. So let's take the vaccine question to begin with. So there have been associations between prior vaccination with MMR, certain influenza vaccines, and BCG all putatively being protective against developing severe COVID disease.

To my way of thinking, there are three possible reasons why that could be the case, and I'll tell you which one I like the best at the end. So one is a phenomenon of immune mimicry, whereby the protective vaccine induces an immune response that is somehow cross-reactive with an epitope on the SARS-CoV-2 virus and/or an infected cell. I personally think that is strikingly unlikely, but remains possible.

The second possibility is, vaccines at a young age have the capability of skewing your immune response for a lifetime. And so, there is a beautiful paper that was published, can't remember if it was *Nature* or *Science* about 15 years ago, that showed that if you had a BCG vaccine early and then you got a helminth infection, your immune response was different than if you didn't have that helminth infection. So you can skew your lifelong immune response based upon prior vaccination history. I think that's more likely than the immune mimicry hypothesis for prior vaccination here.

And then the third possible reason is, we know the theory is there are genetic differences in response to infection. And if you take the example of HIV for example, if you get HIV and you have a polymorphism like CCR5 delta 32, or if you have a certain genetic background like HLA-B57 or B27, either of those scenarios lead you to have less severe HIV infection and disease progression.

It is probable that polymorphisms and/or genetic background are also going to impact the outcome of SARS-CoV-2 infection, and there's a lot of groups that are putting together cohorts to answer that question. So in the case of BCG vaccination for example, those tend to occur in genetically homogeneous populations at different places around the world. And so, it is possible that the populations that are vaccinated with BCG for example, have a high incidence of a HLA haplotype which is associated with disease progression.

So that's the way I think of the vaccine association with less severe disease, is one of those three mechanisms. Hopefully, we'll find out which at some point.

In terms of impact of age, it is correct to say that on a population basis, younger people tend to have less severe disease. It is not, however, always the case. I'm certainly aware of patients who are young, healthy, marathon runners, high-performing athletes, who developed critical illness with this virus. So it's not protective-protective, it's population association.

Why that is? It tends to co-align with co-morbidities. In our experience at Mayo, the overwhelming majority of patients who are admitted to hospital have type 2 diabetes, metabolic syndrome, obesity. And I think that's probably the reason for the association. But there's many, many other possibilities, including genetic factors.

GREGORY J. GORES: I want to stay with risk factors. I know that both you, and Dr. Berbari, and Dr Joyner, can all chime in here. So I'll ask them in series. Asthma, is asthma a risk factor?

ANDREW D. BADLEY: No.

GREGORY J. GORES: Dr. Berbari?

ELIE F. BERBARI: Yeah, I think I agree with Andrew. It's not a risk factor. I guess, if you have severe asthma, and depending if you're taking immunosuppressive therapy, there might be a risk. But I agree with Andrew in general. It's not a risk factor.

GREGORY J. GORES: OK. Obesity--

ANDREW D. BADLEY: Can I just follow up on Elie's comment? So early in the pandemic, there were a significant number of reports that chronic immunosuppression may in fact be protective against severe disease.

And the rationale there is that while you may get the viremic and viral replication phase, the immunosuppression prevents that from being converted to the hyper-inflammatory phase. And as a result of that, there are a large number of clinical trials ongoing with medications traditionally thought of as being immunosuppressive, including tacrolimus, mycophenolate, JAK inhibitors, all kinds of things.

So there's also a large number of trials about glucocorticoids early-- well, at various points in the disease ranging from as soon as you're treated. I think there is some biologic logic behind that. I don't think it's a strong enough logic that I want to give early infected patient tacrolimus, for example, but I think there is some logic in that. And as you apply it to the asthma case, if you're on glucocorticoids, it's possible that could be protective against disease progression.

GREGORY J. GORES: Thank you. Obesity.

MICHAEL J. JOYNER: Greg?

GREGORY J. GORES: Yeah, Mike?

MICHAEL J. JOYNER: Yeah. We now have about 11,000 four-hour case reports, and probably about 7,000 or 8,000 seven-day case reports which we're starting to evaluate. And we'll be able to drill down on this, many of the medications Dr. Badley talked about, we have on the forms to look at. They're covariants, so we're going to try to take a deep dive into some of the mortality statistics that we have in this cohort of people, especially critically ill ones.

But certainly, as we look at some of the more interesting case report forms that we scan every day, obesity really stands out. Age stands out. And really, the usual suspects: diabetes, hypertension, pre-existing cardiovascular disease, pre-existing lung disease in the sense of COPD and other things. Also, pre-existing kidney disease. So just general poor health and age, along with obesity seem to be big predictors of who does especially poorly.

GREGORY J. GORES: Thank you. But that's a select population, right? That's a population of sick people--

MICHAEL J. JOYNER: Yeah, right. And again, 2/3 are in the ICU already. So the people that are avoiding the ICU are, in general, the young people that the Andrew talked about.

And I think the other thing is-- I think I shared it with you guys, a preprint from the blood donor pool in Denmark age 18 to 69. So people healthy enough to be blood donors had relatively low infection fatality rates. Suggesting again, that a lot of the fatalities are going to occur in people that have a lot of other medical problems.

GREGORY J. GORES: OK. And then, sticking with the young people question, there is this question in the news now about this multi-system inflammatory syndrome in children. And we've got a couple of questions about this from our audience. Who would like to take that question on?

ANDREW D. BADLEY: We have not yet seen a case of it at Mayo Clinic. It is my belief that it is an immune-mediated small vessel vasculitis, much like Kawasaki's disease. What is the offending epitope has yet to be determined. It appears to be relatively short-lived.

My understanding of the syndrome is that after patients are diagnosed with it, they develop this hypercoagulable state and the vasculitis. And with anti-inflammatory anti-vasculitis-type intervention, it tends to get better in a matter of a couple of weeks.

Whether or not we're going to see similar phenomena associated with recovery in adults has yet to be determined. But certainly, we're seeing lots and lots of cases of hypercoagulability post-recovery. And whether that's from the vasculitic cause as opposed to a strictly hypercoagulable cause has yet to be determined.

We're also seeing a couple of cases of Guillian-Barré syndrome post-COVID. Again, arguing to a misdirected immune response. So I think it's going to be very important to see how these reports progress over time, and get a sense of the totality of the immune sequelae which can occur post-recovery.

GREGORY J. GORES: Yeah. It's very to note that all these data come from populations that enter the medical environment, right? And so if you look at some population studies, probably the best come from Iceland, where they have everybody genotyped and phenotyped. The risk of illness in children is minuscule, and I think we can reassure people with some of that information.

MICHAEL J. JOYNER: Greg, and I think the issue with children, when people start thinking about when can schools reopen and so forth, isn't the kids themselves for the reasons that you mentioned in the Iceland data, and others. It's that some kid's going to have a cryptic case and track it home, and give grandma, who's on dialysis, a hug. And bad things are going to happen.

GREGORY J. GORES: Yes. Well said, Mike. Anyway, I think we're getting close to time here. But maybe we'll-- Dr. Berbari, we'll just have you take the approach to how Mayo is testing people entering the hospital for procedures. We've had some questions along those lines.

ELIE F. BERBARI: Yeah. Thank you, Greg. So for asymptomatic testing in a health care setting, and our ability to expand the indications now in terms of capacity and better understanding of the shedding patterns, that there are many, many more patients or individuals that are asymptomatic or pre-symptomatic who might be shedding the virus.

We also know that folks who are asymptomatic who are to undergo a major surgical procedure, the co-morbidity associated with the surgical procedure is higher if you're COVID positive. So at the Mayo Clinic and many other centers, we are testing patients before they undergo a surgical procedure, or any procedure, to detect the presence of asymptomatic shedding. If that is the case and the procedure is not urgent, the procedure is delayed until a time when they are better, or they are no longer shedding the virus.

GREGORY J. GORES: OK, thank you. I think we'll close as we've run at the end of our hour here. I would say that I really want to thank all the participants for logging in this morning. I really want to thank our panelists for their outstanding presentations, insights, and expertise. There will be a recording of this webinar, it will be posted on ce.mayo.edu for those who want to look at it asynchronously.

And if you want to look at our next webinar, it will be June 2 at 9:00 AM, where Dr. Sampathkumar will be moderating discussions around infection control as states are reopening. We did have a lot of questions for our panelists about what our thoughts were on reopening schools in this country, when will I be able to get a haircut, these kind of things. But we'll save those for the second date.

So, thank you everybody.