COVID-19 Conversations Webinar: Emerging Evidence on COVID-19 Spread and Treatment

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Dr. Dzau: Okay. Good afternoon. I'm Victor Dzau, president of the National Academy of Medicine. Welcome to third webinar in the COVID-19 Conversations series brought to you by the American Public Health Association and the National Academy of Medicine. This series purposes to explore the state of science around COVID-19 to inform policymakers, public health and health care professionals, scientists, business leaders, and the public. The previous two webinars addressed the science of social distancing the benefit risk analysis of social physical distancing strategies and explored the science available to guide the eventual relaxation of measures. Today we will discuss emerging evidence around COVID-19 spread and treatment.
I'd like to thank my co sponsors Georges Benjamin, executive director of APHA, for his support of this very important effort. I'm also grateful for the input of our expert advisory group co- chaired by Carlos del Rio and Nikki Laurie. You can find all the advisors listed at covid19conversations.org

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This webinar will be recorded, and the recording, transcript and slides will be available on covid18conversations.org

Our next webinar will take place on Wednesday, April 15 at 5 pm eastern time and focus on crisis standards of care during this particular pandemic.

Now I'd like to introduce our moderator for today's webinar, Peggy Hamburg. Dr. Hamburg is a foreign secretary of the National Academy of Medicine. She's also former commissioner of the US FDA having stepped down in April 2015 after almost six years of service. Peggy, welcome and take it away.

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Dr. Hamburg: Thank you very much. So as we move forward together to combat COVID-19 in our country and around the world, one thing that is absolutely clear is that we must leverage and advance the best possible science to help us address the critical questions before us to lead to meaningful, lasting solutions and to help us, really, make

decisions, day to day as we put in place the programs and policies necessary. So I'm very, very pleased to be part of today's webinar. And today we're going to examine some of the newest data available to understand how long the virus remains active on surfaces or in the air. We're also going to hear the latest news about one very promising treatment that's being studied for COVID-19: the use of convalescent plasma, which is now very much in the news. Of course, there are many treatments that are being developed and studied to address COVID-19, some old drugs being repurposed, some new drugs being developed based on new scientific knowledge about this novel coronavirus, and a future webinar will focus on the broader range of new treatments under discussion, since we can't do them all. Today though, we're going to focus on just one of them. And we will also then have a conversation about ethical considerations for using treatments that haven't gone through the rigorous trials that our system typically requires.

So I'd now like to introduce our expert panel. First, John Lowe, the Assistant Vice Chancellor for inter professional health security training and Education at the University of Nebraska Medical Center, and he'll share his team's latest findings with regard to surface and aerosol stability of the virus.

Then Arturo Casadevall, Chair of molecular microbiology and immunology at Johns Hopkins Bloomberg School of Public Health, and he will talk about his work to develop a treatment from convalescent plasma.
And then finally Alta Charo warranty Knowles Professor of Law and bioethics at the University of Wisconsin at Madison. And she will be asking some of the tough ethical questions that are so important in the current situation. So thank you all for being here, and over to you, Dr. Lowe to get us started.

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Dr. Lowe: Excellent. Thank you, Peggy. And I'll just wait while my slides get brought up.
And Susan are my slides live.. All right, thank you so much. I'm having trouble seeing them. So I will just go off of off of your info but so I'm going to talk about the current state of of knowledge and the results of a study that we conducted at the University of Nebraska Medical Center on the surface and aerosols stability and transmission dynamics related to SARS-CoV-2. This work represents the work of a large team and I just wanted to highlight those members conducting rapid response research in the midst of a pandemic as there's very limited limited information. Is difficult and takes a very robust and collaborative team. So I want to thank all of those numbers.

Dr. Lowe: So, context matters in terms of understanding the importance and the value and why we conducted this particular study, and why we're why we're interested in its transmission dynamics and since the

emergence of SARS-CoV-2 and the COVID-19 illness in late 2019 there's been significant debate about trends for the virus, and and this debate is important because it drives national and international guidelines which Dr resource allocation. How, how we do invest to protect health care providers and and ultimately inform the public health interventions that we implement to stem the spread of the disease...

So again, context matters, and I want to set the timeline in terms of events because this has been a rapidly progressing body of information so important to note that as we've, you know, identified that the the SARS-CoV-2 really emerged or reports of its emergence really started late..by February 7 we really saw a landmark report published in JAMA out by our collaborators and partners in China, identifying, you know, broad characterization of the infection across 138 hospitalized patients. What was significant in terms of transmission dynamics reported there is that really documented firm evidence for nosocomial transmission of related to SARS-CoV-2 but but still left wide open the role that aerosol transmission or environmental contamination might be playing in the transmission of disinfection. So, you know, the world watched with great interest trying to pull whatever information we could out of the outbreaks that were occurring in China, atching on to any information that that we could get our hands on and try to use that to inform national and international preparedness efforts in terms of equipping and training health care workers across the globe.

And then in mid February early to mid February we started hearing these reports off of the Diamond Princess cruise ship and a number of other cruise ships reporting significant transmission amongst populations in those cruise ships. This really I think focused our attention and our interest on what might be happening related to this virus, at least with the information that was coming off the cruise ships that was fairly well documented.

We saw significant numbers of cases and community attack rates. So the documented community attack rate in the princess, the Diamond Princess cruise ship, among those that were tested was about 20% of the passengers.And then there's also been estimated attack rates if we had been able to test all of the passengers estimating upwards of 40% attack rate. There's been a significant number of other examples, especially with related to cruise ships, notably the SS Greg Mortimer that that reported a almost 60% attack rate and passengers on that, on that cruise ship. Clearly, indicating that cruise ships appear to be a unique permissive environment for SARS-CoV-2 to spread, and we're curious as to what the different transmission dynamics are that that make that the case.

Some considerations being close quarters and identities of individuals that likely have frequent contact and he crew members that are doing food prep or delivery of items to rooms after quarantine and room

isolation has been implemented. And then of course unknowns about air handling systems and wastewater treatment and systems on those cruise ships as well. So with this in mind we started to prepare and try to decipher, Are we going to implement airborne isolation precautions, contact droplet precautions?
...On March 4 our colleagues in Singapore, led by khalis Mario Muth who conducted some environmental and air sampling related to the initial patients that presented in Singapore and provided some some good evidence, but they were able to take samples in three rooms, a broad set of environmental samples and air samples and and targeted collection of those samples around environmental cleaning, which is important to know. And what they found is that not much SARS-CoV-2 be found in the environment after cleaning. In fact, zero of their environmental samples, with the exception of one sample off of a boot of a health care provider, and none of their air samples came back positive. Then, on March 9 two days later, we have more evidence emerge indicating and this was conducted by a group at the National Laboratories with a series of lab studies really trying to characterize the stability of the virus on surfaces and in the air, specific to SARS-CoV-2. And this group in conducting the series of lab studies really identified that the virus can remain infectious in aerosol for up to three hours in an environment and, you know, and remain in the environment on solid surfaces for a variety of durations. The longest being 72 hours on on solid surfaces such as plastic. But again starting to add more evidence and understanding for us in terms of the role the environment or the air aerosol may play mission of this particular infection.

So the group at the University of Nebraska Medical Center have the opportunity again based on a great deal of advanced preparation to ready a team to conduct environmental and air sampling a fairly robust protocol as patients arrived...in our preliminary eesults of this have been made available publicly on met Rx we're providing the link here so that it can be accessed. I think it's important to note that this work has not been fully peer-reviewed yet. And a lot of the work that I'm going to review, I'll highlight that. When it's not peer reviewed, because this is an important criteria that we need to take into account and and provide that caveat that peer review is a really important aspect to making determinations if research has been conducted dequately for us to make actionable decisions off of. So, this is this is that manuscript and where it's available. Next slide.

So the experience at Nebraska really started on February 17 and went from there. When we received a cohort initial cohort of 13 individuals that were repatriated off of that Diamond Princess cruise ship. Additionally, through later days received two more individuals from that cohort off the cruise ship.And what's important about this, this group and the study that I'm going to talk about is it represents Environment an aerosol sampling study that that crosses a spectrum of illness.

So many of these individuals had mild illness that would only typically require home isolation, others had a more severe illness that would require hospitalization and so we conducted sampling and both of those environments. Next slide.

For the two environments that this is relevant to our two very highly controlled environments are Nebraska bio containment unit, which is where we cared for initial index patients that were cared for at our facility – It's an advanced isolation unit capable of critical care intervention – and then our national quarantine unit. That again represents a residential isolation space which is fairly unique, and we'll get into that. But both of these have similar characteristics in terms of engineering controlS... staff that are trained and robust protocols and how to navigate in the space. Next slide.

So our sampling encompassed sampling in rooms adjacent or rooms that were being used to care for three individuals that were hospitalized. On day 10 of admission to have those rooms were sampled on day 10 of admission for those individuals. And the third on day four of the admission. And then in the national quarantine unit we sampled nine residential rooms, all with individuals that were mildly symptomatic very mildly ill in some cases were, you know, switching status between asymptomatic and mildly symptomatic on a day to day basis, but all of those samples were collected between days five and nine of admission.

And one other thing that is is really important to note in terms of why we conducted this study, aside from, you know, just needing evidence globally to best protect our health care providers and prioritize resources. Here at Nebraska. The National quarantine Unit had always been intended to provide quarantine, that is isolation or quarantine of individuals that have been exposed, but are not necessarily ill. And this situation required that we put confirmed cases with mild illness into the space. And so we for our own interest. We're interested in doing rapid quality improvement quality assessment of product protocols for that type of use, which was a new use case for us.

So the samples that we collected, again, these are fairly uniform across the two spaces, the hospitalized rooms and the residential isolation room. So we collected a broad set of room surface samples focusing on ventilation grates, table tops and window ledges. We also sampled personal items and looking at cell phones, exercise equipment that were used, TV remotes and the like. And also toilets and then we collected two categories of air samples, high volume high flow air samples that were collected in the rooms and outside in the hallways and then also low volume air samplers that were a fixed to the sampling personnel that were in the space moving around.

Important to note that our, our assessment. Our laboratory evaluation

of these specimen ends was done via PCR, similar to the other studies that have already been mentioned. So broad set of results moving quickly so we can stay on time here and broadly speaking, we did two rounds of sampling and the quarantine unit again with those in more of a residential isolation or home isolation type situation. We did find broad environmental contamination, which you'll see through the first half and kind of the second half of this particular chart. We did identify... statistically significant reduction in the level of environmental contamination in terms of samples that were positive between the first sampling and the second sampling, which were days apart. The last three bars on this graph, all the way to the right hand side represent the environmental sampling sites in in the hospital rooms. So in the bio containment unit, and we'll talk a little bit more about those in a second. And so, broadly speaking, and these are just percent positive across all the rooms by site type, Important to note, and really, I mean, the main takeaway here is that we have widespread environmental contamination.

I think to contrast that with our Singapore colleagues that we're really targeting environmental sampling with environmental cleaning. I think that's something that should give everyone a lot of confidence and resolve to implement environmental cleaning, even in the chaos of managing cohort awards or search words related to COVID that it does markedly bring down environmental contamination ...

Notable here. We did find a significant contamination or positive samples on air handling grates, which again, for our purposes starts to indicate the potential of aerosol transmission or transport a virus. window ledges are important finding here as all of these window ledges were greater than six feet away from patients. And then of course toilets, that supports other literature in terms of the the fecal oral transmission potential as well. So here we have results of the hallway air samples and personal air samples. And just to know a significant number of our hallway air samples came back positive, roughly 60%, although these were negative pressure rooms. I think it's important to note, especially when thinking through how to compare this to your operational environment, or the Singapore studies, as our rooms are not equipped with ante rooms and so again this might just indicate the value of those ante rooms and again
airflow is is different for all of these spaces. I think the important thing that I want to note here on this table is in the lower portion of this table for the the mbu which is our hospital isolation. And the, the air samples that have the highest concentration of virus. And again, this is copies of RNA per liter of air are really the personal air samples... which kind of indicate that the personnel in the space moving around the space are are being exposed to viral RNA for sure at a higher level than than some of the surfaces that that we sample.

And so on this next slide. This is a big table. I'm just going to highlight a few things. And then we'll move on because we've got a lot

of ground to cover with my other presenters and but the in room air samples. Really the main takeaway is that 63% of our in room air samples were positive by PCR. To to have three of our air samples collected outside of six feet. So again, this was in the hospitalized individuals rooms were positive by PCR as well. Again, supporting that notion that at least viral RNA is being carried via the air greater than six feet and then the highest concentration and then...contamination samples was really identified in a room where an individual was on a low flow nasal cannula with one leader of oxygen. And so again, that's something that is is an area of interest or follow up as well. I'll touch on that in a minute. So broad conclusions to move quickly we identified and documented ubiquitous environmental contamination, not necessarily linked to symptoms or severity of illness.

Again, I think it's important to couch this in the findings of our Singapore colleagues on the value of environmental routine environmental disinfection...Our PCR positive air samples outside of six feet, I think, provide additional evidence of the potential of aerosol transmission. But again, we did not evaluate the particle size or distribution potential of those particles in this particular study with our methods and as already noted the value of environmental disinfection. So areas of interest that we've heard from colleagues around the world and that we're very interested in as well is starting to investigate does do all of these environmental and aerosol samples contain infectious virus. I think this is the next domain of investigation that really needs to be sorted out to help inform protocols and to determine the particle size for the ... RNA and infectious virus again how far those particles like to carry likely to carry that virus. What is the infectious dose? So how can we translate in the event that we do find this information, what does that mean for infectivity or infectious risk?

Looking for longitudinal studies of viral shedding throughout the course of infection. So we have a greater understanding of the transmission potential for asymptomatic pre-symptomatic or different stages of severity of illness. And then we've heard a lot of interest, and we know a number of groups are looking at, the role of various oxygen delivery systems and generating aerosols in the clinical space.

So one study has come out since ours was reported again by our colleagues in Singapore...where they've actually looked at this fractionation of aerosols and identified positive for our for viral RNA. In aerosol particles greater than four microns in between one and four microns. So again, further evidence that kind of takes the next step from our study and looking at the potential for aerosol carriage of the virus and the RNA.

And this is my final slide, I think it's important to note, as we've been helping folks translate our findings that again, have not been

peer reviewed yet is one, the importance of environmental cleaning really looking at ways to protocolize that and do it regularly. For us, this has given us resolve to implement negative pressure and barrier precautions wherever we can. In the care for suspected or confirmed COCVID-19 patients and to really look at staff flow and can we minimize the number of health care providers that need to [interact with a patient].

And then again, I always want to point out that, as we go through those, you know, cleaning, environmental controls, administrative controls, the bottom thing that we go to when we look at hierarchy of controls is PPE. So these other domains are more effective, but we tend as health care providers to pivot or first and foremost to personal protective equipment, which is important, but some of these other controls have higher efficacy. So that concludes my remarks. I'm, I'm happy to hand it back to you, Peggy.

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Dr. Hamburg: Well, thank you very much, really interesting, important work that reminds us about the importance of doing real time research to inform our policies activities and programs in an ongoing way.

We Will turn now to rather different but equally important topic, having to do with therapy and I'll ask Dr. Casadeveall to tell us about his work on convalescent plasma as a treatment for COVID-19

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Dr. Casadevall: Thank you, Dr. Hamburg. So the first slide will just be convalescent plasma for prophylaxis and treatment of COVID-19. Next slide. So the first question is what is convalescent plasma? Plasma is the liquid in the blood that holds the blood cells. It is obtained by separating the cells from the fluid. Now, when you look at the literature sometimes this product is referred to as sera and sometimes it is referred to as plasma. That just has to do with whether it contains clotting factors. It doesn't affect the antibody content, the antibody content is staying involved. However, today in 2020 we use plasma. We don't use sera and this is a way that I will refer to it, even though, when you look at the literature you will see the word sera and serum therapy used over and over again.

It the plasma can be obtained by donors ... and it is obtained by standard transfusion practices, and that's important because people need to know that this is a very well-regulated industry that really is doing and that they have the capacity to take out the plasma and to give you a unit, just to get shown in the bar on the right part of the slide, you will see a diagram that breaks up the red cells.... Those are the white cells and then the plasma is much of the volume of the blood, which is about 55% of the total volume.

So the principles are straightforward. When you have an infectious disease, viral infection and you get better, there are usually antibodies in your blood. These antibodies in the case of many viral infections can .... So when you recover, you have these antibodies, and then you have a blood draw. And in the plasma, these antibodies are found that can then be used for two major ways of combating COVID-19. One of them will be done for prophylaxis. You give antibodies to people and you give them immediate immunity after they get the infusion. They have these antibodies. ...they can be used in therapy, and we'll talk about both.

So it's important to know that convalescent serum, notice that here I'm using the old terminology, or plasma, has been used in past epidemics. There are hundreds if not thousands of papers in the literature in which a serum was used. It was used [in epidemics]. If you look at the data from the time the doctors thought that it worked. It was used to stop outbreaks, such as ...measles in schools, and it was used for breaking up epidemics .... It was use on polio when he struck in cities. The practice ended pretty much after the 1950s, for two reasons. One was the discovery of blood borne pathogens which were not done previously. And by the way, for which was created today. And the other reason was that many of these diseases in particularly childhood diseases began to disappear with the advent of vaccines.

So the important component in plasma is a specific immunoglobulin. Immunoglobulin is a scientific word for the word antibodies, so the, the plasma has a lot of antibody input. Now when you recover it has antibodies that can kill the virus. These antibodies includes GM and I GG. Gg has a half life of over 20 days. That's important because it will suggest that an infusion of plasma could provide immunity for a while, for a few weeks. It is a complex mixture of antibodies, different classes of antibodies. Antibodies ...from parts of the virus. And that's important because often neutralization works best if you can hit the virus at multiple places. The effective immuno governors fall into two categories: neutralizing antibody that's antibody to kill the virus; but there is also a set of antibodies, known as long neutralizing antibodies. They can mediate protection by other mechanisms, including binding to the receptor ...

So we do have some experience with the use of convalescent plasma for two other coronavirus diseases, SARS coronavirus which occurred in 2003.There is the best study came out of Hong Kong in which at patients with SARS coronavirus were treated with convalescent sera. And they documented a often almost three fold increase actually three four plus increase in this ... among those that which we could combine ...sera.

I stress to you that even though these numbers look good, and even though they may have statistical significance, this was not a prospective clinical trial. This was a series of cases. So [it's

anecdotal] to see how well they did.

And for SARS coronavirus there has been anecdotal use. The problem with that has been finding donors. It turns out that MERS coronavirus often doesn't generate very high titers of antibody in survivors, and what's been found ... will tolerate it for the efficacy has been difficult ...

So China very rapidly moved on to use convalescence sera against COVID-19 and there are now, as of yesterday, three papers in literature and in very respectable peer reviewed journals. The one in JAMA described five critically ill patients treated with it. Well, there is the paper and... describes another set, I believe you see the 10 or 15 patients ...Describes five patients. So the data is starting to come out of China, data are encouraging. the data are positive, but again, one needs to look at this publications with care and with rigor, because they are not controlled clinical trials in the sense that that we often do in order to establish ... The Italians are using and even though it's not in the literature, I can tell you from reading from my Spanish that one on the left says last month and see, on which I interpreted as "plasma works" and the other one Says that that was so. So that the first results were positive. So again, when you look at the experience for northern Italy, which is not in the medical literature yet, is appearing in newspapers. The data are encouraging

So we have written two papers on this...in the journal Clinical Investigation. The journal worked really hard to get the stuff reviewed and published, often within a week. The paper on the left sets out the big picture ,sets out case for doing it. The paper on the right was just published yesterday or the day before and it reflects everything that we have learned in the past month trying to put together a trial. These papers are free for download. You just have to go to their website and download. The paper on the right includes things like what those to us, what will be the flow by which you will identify individuals to donate, includes a risk benefit analysis of the use of convalescence sera. I'll say a couple more words about it. So here's the workflow and it is complicated, it is complicated, but I'm just going to basically work you through it. And on the right, you see a report. That was an NBC news of a donor donating two units of plasma in New York City. So the way to work through all this. If you're more interested, you can download the paper, take a look at it yourself. But basically, we need people, people who recover from COVID-19. That is, they had a documented test and they had the disease. Then we have to wait at least two weeks, then these people need to be tested to make sure that they have cleared the virus by PCR. One of the problems that we see is that a significant number of people still have a positive PCR [after] two weeks, we don't know what that means.... It could just be reflecting RNA in secretions that is remaining but you have to be cautious with this virus. Therefore, we

are not allowing people to come in and donate blood until they are shown to be negative. So that is putting a bit of a logistical hurdle in getting lots of donors, but we think that as time goes on, and we have a lot more people who recovered and we have a lot more people that are now three to four weeks out that there will be a lot more ... logistical problems will become easier when this plasma is collected in a facility where they collect plasma is tested for ... all the infectious diseases and then it is typed and then one has a unit of plasma that is convalescent and you can potentially using on an individual. It needs to be ABL compatible with the recipient and all this is the workflow that we have arrived on after several weeks of learning how we're going to deploy this. So the FDA. These are from their website, the FDA has moved very quickly on this and I compliment my FDA colleagues, they being super, they've been, our conversations are going back and forth. And you can see how rapidly this is moving. On March 24 we have we had approval for compassion with us for April 3 Hopkins have been granted permission for clinical trials convalescent plasma high risk individuals, April 3 FDA allowed expanded access and yesterday they provided additional recommendations. So this the FDA website is a rich place to look for details on how to implement this. Okay, so it's always important to acknowledge every medical procedure has some risks, and we have known risks and theoretical risks. So the known risks are transfusion reactions and some rare risk of infectious disease. These are very low, but they are not zero, and they would happen with the use of plasma and they are associated with use of plasma in the medical arena where plasma is often used in surgeries and other procedures. And then there is a theoretical risk that hasn't been seen yet, but we need to always keep in mind the possibility and that is the antibodies can trigger ... inflammatory reaction that could make things worse. I stress that the data from China and the anecdotal data that we're getting is that this hasn't been seen, but perhaps we need to be on guard because if more and more people can treat it, you may be you may see some of these effects.

The ... paper that I was talking about in JCR, you could look at it, has a formal risk benefit analysis. I suggested the benefit is based on the risk for all age groups. So where is the current status compassionate uses been done in the United States places like Hopkins gearing up to do formal trials, many countries are deploying convalescence sera. And here, this is just taking from the news, includes the United Kingdom, France, Italy, Spain, Argentina, Panama, etc. And ...I mean the many places that have contacted us and we have shared protocols. This appears to be a worldwide effort. Currently, and one only hopes, is that all these countries as they get any experience share with others because we need to learn how to do this. So clinical trials and preparation include at least for prophylactic use early therapeutic use that is, can plasma prevent people from getting worse? Can plasma prevent people who are having shortness of breath from having to go into the intensive care unit? A late therapeutic use that's comparable to Compassionate Use: people that

are [in ICU] that are on respirators. Will they benefit from this? I will stress that most of the use that is simple literature from China has been late therapeutic use and even though antibody always works best early I'm encouraged by the fact that they are reporting some positive results with like a therapeutic use, which is a situation in which often antibody doesn't work. And then there are a pediatric protocols in development because it is clear that kids are getting this also and that they may need it.

Today, the major problem is logistics, implementing this on a large scale. We don't have mechanisms in place for taking convalescent plasma. We have great facilities in place for blood drives and other blood products. But the problem here arises that we need to get a particular population, which are recovered people. You need to test them for the virus and then you need to ask them to come back in and the New York City, you see that picture. This ... community has been incredible on organizing itself and identifying donors and providing people for blood donation at the various places that are taking donation information. This always comes up. You want to donate. How do you do it? The Red Cross is collecting plasma across the United States. In New York, the New York Blood Center is collecting plasma and then you have the specific institutions that are using the transfusion facilities to collect plasma, for example, Sinai in New York City ...and Hopkins and we have a website that you can go to known as CCP 19 dot org and there is a mechanism by which, if you know that you had COVID-19 and you want to donate then we are collecting some information to match you and your zip code with facilities for donation.

Closing thoughts: so history provides strong encouragement for its use. It is supported by strong basic science. We have over 100 years of knowledge of antibody reaction. I should point out that the first Nobel Prize was given ... for serum for this is all this is Plasma therapy is relatively safe. However, I caution that that COVID-19 is a new disease. This is a new virus. And we won't know how well this works, until we carry our formal clinical trials. The anecdotal evidence and the patient case here is encouraging. But we need randomized controlled trials to know if when and how to use it. The challenge today is logistical .... We're learning how to do this better, we will have a lot more people capable of donating in the next few weeks and I think today plasma is a very scarce commodity, but I think it will become more plentiful as the days go by. That's it. Thank you.

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Dr. Hamburg: Thank you very much, and your closing thoughts. I think are a very nice transition to our next speaker. Alta Charo, who is our legal and ethical scholar. Before she begins, let me just remind you also, though, that there will be a future webinar on some of the research and development that's going around going on concerning other

potential drug treatments and stay tuned for that. Now, let me turn to Alta.

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Professor Charo: Hi, thank you very much. And greetings out there. I want to start very quickly with background that I suspect many of you know, but just to make sure everybody is on track that. There is a usual process for developing therapeutics that involves a series of research endeavors. Starting with in vitro and animal often animal preclinical work and then the development of a protocol for trials that typically involve a control arm. It could be a standard intervention versus than a standard plus or it could be to see about there's really no treatment available and then a very slow stepping up in terms of the number of people who are going to be recruited and a change from safety primary to safety and efficacy primary. Along the way, in terms of what you're looking for are the trials are usually prospective and randomized in order to make sure that you are actually getting the results that I'm getting the result that you need, which is to understand the intervention itself being effective or not.

Once this has been done, the FDA can give approval for the product marketing, but its approval is in conjunction with a variety of variables, particularly the kind of people, the dosages, and the country indications and all of those on the so called label. Once a drug is on the market, the companies that are selling it are free to advertise it, but only to market it for those uses, populations, dosages, etc. that were part of the approval from the FDA. This doesn't mean that physicians can't use it for something else. This is very typical. Physicians may prescribe so called off label and sometimes it has a very strong scientific basis, based on experience over the years that's been reported in medical journals, but the companies are not allowed to begin marketing it for those things unless they go back and do additional testing to confirm that it is safe and effective for them. And then they can get a supplemental label.

Now under an emergency situation, we don't necessarily have the time to go through those very careful steps, and there is a provision for so called emergency use authorization. It is important because although physicians do have this kind of off label privilege, it also will allow for unapproved products to now be moved into use or for unapproved uses of it approved product that is an off label use to be to be advertised. And it is something that has additional kinds of of attributes, including rather importantly that it offers liability protection to those who provide these kinds of products. You know it's it's not medical malpractice to do something off label, but it can suggest to some people that this is less than meeting the usual standard of care. Liability protection is very helpful for the providers and the federal protections will also include state actions.

Now to get to the emergency use authorization. There is a rather complicated procedure, having to do with determinations related to a chemical, biological, radiological nuclear threat determinations made by Homeland Security, defense department or ... HHS, followed by the HHS Secretary now. Having concluded that the circumstances justify an emergency use authorization, for example, that there are not good products already available to treat whatever this risk is and only then is FDA allowed to issue the EUA, and it's notable that usually this is done based on some amount of real evidence of safety and efficacy based on preclinical work in vitro and animal, some anecdotal. We've seen an EUA now issued for to drugs were actually a lot of that pre clinical evidence just doesn't really exist for this new use. Nonetheless, just about 10 days ago issues EUA ...There are some extra protections. There are fact sheets that providers must have that will highlight the known risks and drug interactions, but again, it's not clear that the risks in this particular context can be well understood, and we do know these particular drugs to have some significant risk factors to them. Also under EUA the drugs can be distributed from the Strategic National Stockpile. It's aimed at people who are able to give consent. That's adolescents and adults. We notice that Dr Casadevall mentioned pediatric needs, and that complicates this consent process.

But another important limitation is that it's used on EUA when a clinical trial is not available and not feasible. The idea is that if you've got clinical trials that will actually tell you if this works. That's where we should be going first. But conducting clinical trials, which is crucial for truly understanding what will work and for whom, during a pandemic has some significant challenges. One of them is understanding what the risk benefit ratio might be Dr Casadevall pointed out that for the plasma transfusions, that the risks appear to be fairly low compared to the potential benefits. But for any kind of new use or new product, it is by definition, going to be more difficult to estimate risks and benefits in advance.

The second has to do with which people you're going to treat as research subjects, the people who are sickest maybe it the greatest need for this new emerging option. But number one, it may not work as well for them as it does for those people who are at earlier stages of disease. And second, they are typically people who have other problems, other comorbidities, and therefore are going to be complex people for whom, it'll be difficult to tease out how much of the response is due to the intervention and how much is being a complicated by their underlying conditions. That would suggest then that you use instead a population of people with a milder form of the illness. And that can solve some of those problems, but at the same time, it doesn't give you the information you really want often, which is, can you use this as a rescue therapy for those people who are [extremely ill].

It is complicated to get consent to participate in a research trial. Some of these people are now suffering from some degree of cognitive incompetence because of the effects of the disease. And in this particular situation of an infectious disease, we've seen many, many hospitals and institutions determine that they simply cannot allow visitors to stay with the patient. Family members who typically would be available in other hospitalized situations. This makes it hard to find the appropriate surrogate decision maker to allow somebody to be placed into her clinical trial. It can also be difficult sometimes to think of how to reach them ...to communicate. Although it's helped by things like the Zoom
medium we're using now, it's not the same as the kind of personal interactions that ordinarily would take place. Now consent can be something that we get rid of in emergency situations. Typically, these have been a trauma situation, a car accident and you need to have test for let's say it's a new kind of synthetic blood product. And there's simply no time to be looking for consent from anybody, but we can also see how they could be used in these circumstances. So you could use the special protocol for emergency consent, it tends to be limited to life threatening circumstances. So now again, we're talking about the sickest population, not the kind of mildly ill population. And it involves at some point some degree of notification to the community that this is going to be going on that some people are going to be put into a clinical trial for this new therapeutic intervention, without necessarily knowing in advance and without their surrogate decision makers, knowing in advance that they're being recruited and others might be prepped on the control arm. Which here would need all the kind of current support mechanisms that are obviously a difficulty in community notification when you've got a pandemic that's as broad as this, as opposed to a an isolated clinical trial in a single neighborhood or a single region.

There were other kinds of challenges that have to be met before one can continue on with the effort to do the Clinical Trials. Trials are typically approved, not only by the FDA. But by a local Institutional Review body. And that process has often been criticized as being overly lengthy some IRB are well set up to have a quick response, others not. So this can be something that slows things down without careful selection and complete information immediately to the people on the IRB so that they can evaluate independently risk benefit and recruitment strategies. Choosing a site for the trial. So that you can in fact use emergency consent procedures can be very, very important. And next, probably the biggest problem really is the balance between using these therapeutic interventions off trial. There is a kind of a core dilemma with clinical trials in the United States in which people sometimes simultaneously in their own minds but certainly as between populations you being a research subject, either as being a guinea pig and feeling like they've been exploited or viewing it as an opportunity to get the best and newest thing out there. And in

circumstances like this where there really are no good therapies available, the chances are that there's going to be a lot of interest in trying whatever seems to be the newest intervention, regardless of whether the risks are yet well understood. That means that it can be very difficult to get the control arm. That is, how do you get people to agree not to take the intervention and be part of a clinical trial when their perception, even before it's been proven to be effective, is that it might be effective and we heard already about the historical information that suggests that it might. One way of responding to that has been the expanded access programs. We've seen these before, during the HIV crisis, beginning in the 1980s, so called parallel track was created. The idea was what clinical trials where people are really going to have to have a control on so that we can actually see if the therapy is working as compared to standard care. But if you're not near a clinical trial's site or their clinical trial has already recruited a full cohort of subjects, then you can get access to the new intervention off of this expanded access program. It's very important to make sure that the expanded access program doesn't swamp, the clinical trials to the point that you can no longer do the kind of prospective, randomized work that's necessary in order to really determine if this works. We have had some very notable failures of interventions that people grasp that of the bone marrow transplant for breast cancer that had not responded to chemotherapy is a good example where it's simply made people more miserable and sicker, rather than helping in any way.

Once your clinical trial is under way and especially against this backdrop of some degree of panic and rapidly changing information, it can be very hard to maintain what's called clinical echo voice that is a moment in the clinical moments in the clinical trial when you truly don't know which is better, standard or the standard plus intervention. Because the moment that you have moved beyond echo points and you really think the intervention is having a good effect, you have to ask, is it still ethical to recruit people into a control arm, and this is a subtle problem because you may have intimations of effectiveness but not yet the kind of statistical validation that you need to be confident about those results and often it's important to have an independent group of people, a data monitoring board that can make these kinds of judgments, a little bit more dispassionately. Last on this particular slide, I want to mention that it's really important to manage public expectations as soon as there's any advertisement of any kind of intervention. There are already some examples of fraudulent offers out there of so called cures or prophylaxis. And we're seeing even stem cells, stem cell quote unquote therapies being advertised. So once we begin talking about possible interventions that will treat, it's really hard as a communication strategy to make sure that the public understands which things are really under investigation and which things are probably completely fraudulent. Next slide.

So, as you heard already Johns Hopkins has gotten the okay now to start testing these blood therapies and again, as was mentioned just yesterday, the FDA already began to issue recommendations that will help construct these kinds of things having to do with the pathway which patients are eligible and what kind of record keeping is needed.

I want to conclude on just a few extra considerations that are aimed not at therapeutic interventions for people who are sick, but for prophylaxis. This is a different kind of problem because here you've got a subject population that is healthy and so our tolerance for putting them at risk tends to be lower because we are not nearly as confident that there's going to be a benefit for them. And you still need to make sure that if you do have such a clinical trial that the people in the control group have Standard Precautions and are not abandoning them and the people that are in the intervention group particularly are not abandoned Standard Precautions. This is why, for HIV clinical trials, for example, it was very important that those who were testing new drugs continued to maintain safe sex practices in order to make sure that they would not put themselves at added risk. Of there's going to be a need to select the population from a high risk region. Because you need to quickly have a population of people where you can see a significant difference between those who had the intervention and are now, we hope, not getting sick, and those who are continuing to get sick, which makes this clinical echo points problem and when to stop the trial even more problematic and when to move on to try to give prophylaxis to the widest population possible. In some cases, you might want to ask questions of who should get the prophylaxis. First, in some cases, you might want first responders, the medical personnel who are exposed immediately, including and also, perhaps, police and fire to be given higher priority when it comes to the prophylaxis. But remember, as soon as this is available, there's often going to be a public demand for it.
And that demand may easily swamp the availability of the prophylactic intervention, which makes this question of prioritization very important. I'm going to stop there because I know that you want time for asking questions, and thanks very much.

01:01:36.660 --> 01:02:32.130
Dr. Hamburg: Well, thank you. I think that was a very, very useful and efficient overview of a lot of important and complex issues about the challenges of doing clinical research. In this kind of a crisis that is so marked by both a sense of urgency and a lot of uncertainty.

I'm starting to get questions from our viewers and so let me, I was going to ask a question. My own. But I think since we started late our plans right into the questions from from our viewers and and Dr. Lowe as we're keeping you busy, a follow up question. Someone asked if you could discuss more about your concerns with the FDA and the okay for the UAE for hydroxychloroquine probably won't surprise you that you're getting that question.

01:02:32.970 --> 01:02:40.380
Professor Charo: I'm sure and but there's a limit, there's a limit on what I can say, because I don't have all of the data that was in front of the FDA. But typically, there is more information from both in vitro studies and from animal experiments or from a wider range of anecdotal reports before the FDA will use that information to justify the emergency use authorization. In this particular case, it seems like the anecdotal reports were very limited number and the in vitro evidence, I haven't even seen particularly, so there was some surprise that the EUA was issued, but considering the publicity that these drugs were already getting and the pressure from some members of the public to obtain them to self treat even at some expense to their own health. Unfortunately, it became rather important. I think for the FDA to try to step in and have some degree of control over what's going on, and certainly getting factsheets out as quickly as possible, maybe have some small help

01:03:42.510 --> 01:03:59.430
Dr. Hamburg: Thank you. Just a quick follow up. Someone else was asking about is there a an established mechanism for distribution of products that are approved with you as, is it a specialized route or does it go through the normal avenues of physician prescribing?

01:04:00.450 --> 01:04:06.720
Professor Charo: You know, I think that, Dr. Hamburg, I think that you're probably in a better position to answer that than I am, having been the commissioner at the FDA. I know it comes from the strategic stockpile. But perhaps you can answer that question.

01:04:11.130 --> 01:04:45.060
Dr. Hamburg: Well, I think it is available through the strategic stockpile. And I think it also can be available to other mechanisms of of care. So let's, let's move on then. Thank you. Other questions that we've gotten...There was a question about how does the work you're doing with convalescent plasma relate to some of the therapies that are being developed for monoclonal antibodies. And I guess you know to elaborate on that question. Do you see the the convalescent plasma work as sort of a bridge to other drug therapies that would be logistically easier? As, you know, in terms of administration and collection development of the materials, or do you see all of these potentially going forward in parallel?

01:05:09.030 --> 01:06:03.840
Dr. Casadevall: Absolutely. I think that I think that today on any groups are making monoclonal antibodies already. And in fact, there is an effort to to collect ... sera ....by the pharmaceutical industry that will actually be a pharmaceutical product no different than the hyper immune serum that we have today. The way I look at commerce and sera medicine is available today monoclonal antibodies will take once

at least to be available for clinical trials and the ...intravenous gamma globulin is also going to take many months because then it just, it just needs a development pipeline. So between now and then, we think that the blood of those who are recovered may have antibodies to can help those who are getting sick.

01:06:06.270 --> 01:06:25.020
Dr. Hamburg: Thank you very much. Now a question for Dr. Lowe...There was a concern about what do we know about whether the detectable RNA is actually likely to correlate with infectivity.

01:06:27.180 --> 01:07:02.370
Dr. Lowe: Yes, I think that's one of the questions that remains unanswered. And so one of the things that public health officials and clinical leaders are are having to navigate is what does this evidence of positive RNA in different specimens and different aerosol droplet or particle sizes mean in terms of translating that to practice? So I think we're all walking that balance of there, there seems to be an emerging body of evidence that the virus can be carried on droplets. But we're still lacking that definitive proof, proof of infectious virus in those droplets.

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Dr. Hamburg: And a follow-up practical question: what what do your findings mean for people who are caring for infected individuals in their homes in terms of strategies for decontamination and reducing risk exposure?

01:07:20.790 --> 01:08:06.270
Dr. Lowe: Absolutely. So again, I'm gonna phone a friend back to NIOSH and to that figure, that upside down triangle of the hierarchy of controls. So NIOSH did a great review of masks and home isolation and found that it doesn't necessarily convey any protection within that household across a number of studies. So I think if we look at the bottom of that of that pyramid, right, PPE, we're better off implementing you know distancing, geographical or spatial distancing, and cleaning. If we can implement those it connotes more protection than just having someone who's infected wear a mask around people who aren't. If we can physically separate them and we can clean that space regularly, it's going to have a better result.

01:08:07.140 --> 01:08:34.350
Dr. Hamburg: Okay, thank you very much. I'm back to you, Dr. Casadevall, with a question about what work is being done on post infection markers of COVID-19 infection that can be used to identify potential plasma donors that were not tested at the time of active disease? And I guess this also gets us into the whole area of serology tests and and their utility.

01:08:35.550 --> 1:09:41.010
Dr. Casadevall: So a tremendous amount of work has been done and it's been done by many groups at the same time. And the idea here to clearly note is, every, every unit of plasma is different, and there must be universal ...So if you could identify the unit supplies that are great, they're much more likely to have a better outcome. So that require establishing virus control session tests with the coronavirus as well as developing earning from the serology which are the good antibodies, whether they bind, what is the right cocktail. I can only tell you is that this is a very hot area. People are working on it very hard and hopefully this information may even become available doing what I call the convalescent plasma phase of fighting against COVID-19, which is the early phase. And it was to inform what follows the interview ... on that will hopefully be available later this summer... But it's a hot area.

01:09:42.420 --> 01:10:40.890
Dr. Hamburg: Thank you. And maybe I'll just use that to go back to Professor Charo for a moment. There's been some discussion that with modifications and the emergency use authorization approach and and some of the different products. Now turning to diagnostics and serology tests. While the FDA has warned some manufacturers about the need not to make claims that they can't actually justify in terms of their product, some of these serology tests are in fact not going through the the sort of more traditional EUA process. I'm wondering if you have some perspectives on that. If you know sort of why that determination might have been made. Or some some thoughts and how you think that may play out over time.

01:10:44.250 --> 01:11:43.440
Professor Charo: Well, certainly I think this discussion goes back several weeks. It feels like several years now to the lack of tests available.And there was a fair amount of publicity, suggesting that the fault would lie entirely with the FDA's onerous process for obtaining and emergency use authorization for a diagnostic test.I think the more time that goes by and the more investigation that goes by, we understand. There were many elements that led to the slowdown in obtaining those tests. And there were a few that had to do with the kind of process of submitting information and getting it properly into the FDA. That needed to be changed and more change, but I'm a bigger change that came was one that now does offer a few dilemmas for us. And that is that under the previous system you first had to submit to the FDA, the diagnostic testing wanted to use and data that supported its analytical validity, and its clinical utility and the FDA would then respond with a yes or no about whether or not you could go forward.There, that's not been turned on its head in which people can now develop, test and begin using them without even having gotten any kind of FDA involvement there is a few weeks afterwards, where you're supposed to then try to provide the information that would justify its

use. Secondly, there had been some controls on the quality of the laboratories that were doing this so that only those laboratories that had been shown in the past to meet the tests that prove they can do complex work would be eligible for producing the diagnostics, and the new policy has now brought in the range of laboratories for a variety of reasons. When it comes to the serological testing, we're going to be an interesting kind of situation because it will not necessarily be an existing product for which we're talking about a new use where at least there's some history of the risk benefit balance as prescribed, but an entirely new product, which needs to be reviewed and approved and again this can come up under EUA, but I think it ups the ante on the uncertainties surrounding it. And I think it is a little bit more nerve wracking. When you don't have to have any submission to the FDA prior to beginning its use in a in a compassionate or expanded access program which will expose many, many people to the new product.

01:13:12.690 --> 01:14:13.920
Dr. Hamburg: Thank you very useful perspective, it might be interesting. We're getting a lot of questions about Compassionate Use and where that fits in. And actually, you know, we have the opportunity for Dr. Casadevall, who's working on a clinical trial right now. Where it's important, as you noted to do the controlled studies to get that the, the, you know, robust answers about how this works. ...But also have intervention that is available through Compassionate Use. Professor Charo made the observation that ... there are concerns that as these drugs become available to providers and patients to other mechanisms that it can potentially compromised, the ongoing clinical research. So I thought, you know, maybe ... a real world perspective from you, Dr. Casadevall and then maybe you'll think of some other comments you'd like to make

01:14:15.300 --> 01:16:01.170
Dr. Casadevall: I think you're absolutely right. I think that, first, we have a scarce product. Second. We have a lot of people who need it. And I see as as people are quite sick. I think that is going to be very difficult to do trials in the very sick, simply because Compassionate Use is available and maybe that's that's the way it should be. I do think that early on for when people are just getting symptoms it may be possible to evaluate how well this prevents pulmonary deterioration, and it should be possible to do the trials in prophylaxis because they are we really looking at preventing people from getting ill and hopefully for preserving the our entire infrastructure people, we need to go to work and as well as people who are getting exposed to this horrible disease. I will tell you that it every single epidemic. And I looked at convalescent sera use, doctors in the middle of it, use it. And they often ... feel it works. And then after it happens people do retrospectives trials and they criticize it for not having done a prospective trial. And I think you are beginning to see how difficult it's going to be to do that with a product that is relatively safe and yet can provide and has a history,

or a very encouraging history, but we're determined to try. I think we need, we have a responsibility to try to to do good medicine to do good science because we're going to be at this for a while. And if we can figure out how to do this right up front, perhaps we can help a lot of people in the, in the next few months, and maybe years.

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Dr. Hamburg: Thank you. Professor Charo, do you have some additional thoughts on this issue?

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Professor Charo: Well, just a very quick clarification that the words Compassionate Use don't actually appear in the statutory authorities. What it is is really a permission for the use of an unapproved product that ordinarily cannot be placed into interstate commerce. I know that's kind of typical its population. And it is really designed for very limited number of cases, which is why when you've got a situation like the one here, you move to a broader program, the so called expanded access program and here we may find a compromise. It's not because ... If the clinical trials, need to be developed using a population of people with a milder form of illness, so that you're more confident about the results that you're seeing and able to tease out the intervention versus everything else.
Then you might then find that compassionate use on a broader scale is going to become available to those people who are in extreme illness and or really close to death. That population is the one that may need it the most. But their, their situation is so complicated now that it would be hard to evaluate the effectiveness of this particular plasma transfusion. If we use them in the trial, as well as now enhancing all of the problems of of ethically recruiting them into such a trial. Well...

01:17:29.790 --> 01:18:50.160
Dr. Hamburg: I think another issue that emerges and maybe I'll quickly turn back to Dr. Casadevall and then there are a lot of questions on environmental exposures and aerosol transmission. So Dr. Lowe, we're coming back to you. But, um, there, there is some sense that we can learn a lot from the use of these products through Compassionate Use or the expanded availability that has that will come with the emergency use authorization getting reports from physicians and patients about the use and so called real world data about, you know, disease progression sounds promising on one level, but when you're really talking about getting robust scientific answers, obviously, it's very challenging, especially for disease where most people get better. Anyway, so I'm just wondering, as you're going about your research, Dr. Casadevall, how do you think about the role of this other sort of approach of more observational data nd reporting as compared to your controlled clinical trials?

01:18:50.490 --> 01:18:55.920

Dr. Casadevall: Dr Hamburg, I think you're absolutely right. In fact, when you look at the reports that are coming out from China and they will in you learning a lot from observational studies you learning a lot from what happens to an individual when you infuse them with plasma. You learn that the Iranians reduce you learn that in some cases they getting out respirators. However, they are not control and we need to be very cognizant of these biases, but every time that you use this products there is learning that occurs... I'm encouraged that that it may be possible to do very good observational studies, if you have, f you have a limited product. For example, in the way you're using it, you may be able to compare it to other people who are not receiving it. And I will also throw something out for you to think about everyone in this for. Think about it. Many of the great drugs that we use today never went through these kind of studies. It was no randomized control trials for penicillin. Doesn't mean that it doesn't work. No, it means that we have learned how to do and we have learned the risks that come with biases and things like that. And we try to minimize them with randomized control trials. But I think at the end of the day, we all try to be as good observers and to try to learn from this because we know that these clinical information can be translated and used in the future.

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01:20:20.820 --> 01:21:25.830
Dr. Hamburg: Thank you, very informative. Well, I'm told that there now 600 questions in the queue. And we've got 10 minutes left, so I don't think we're going to get to them all. I apologize, but a lot of questions were stimulated by your remarks, Dr. Lowe. And let me just see if I can get a few of them out for discussion. Questions about sort of what's, what's your sense of the relative prominence of different modes of transmission? Is it still mainly respiratory droplets that we need to be concerned about, or is aerosol? You know, something that that really also is a dominant mode of transmission. Does that affect how we think about our own behaviors? The wearing masks, the distance for social distancing when going outside, etc. So, and, and also maybe if you can just quickly sort of compare your experience with this novel coronavirus and its modes of transmission to flu and measles as well.

01:21:27.030 --> 01:25:02.430
Dr. Lowe: Yeah, so a few. There's a lot to unpack there. A few things that I want to highlight related to the conversation that we just had with Dr. Casadevall and Professor Charo, I think this also, the broader conversation underscores the value in the need to develop multi site rapid response clinical trials networks ahead of emergencies, which is incredibly complex and difficult to do. It's hard to get all of those partners on board when there's not an emergency to respond to, to get the the review frameworks and the regulatory frameworks and agreements in place when there's nothing, there's nothing to investigate at the moment. We do have one that was

established, the Special Pathogens Research Network across the US that has 10 sites that committed to this.And I think it's important to note that this network was one that got the ... clinical trial up and running within 72 hours of the first patient arriving at one of those sites and so I think this is something that that underscores the importance of doing preparedness and planning, especially with respect to both clinical research and the regulatory frameworks for such research so that we can implement really broad rigorous studies that can be done. It just requires a lot of time and effort, not knowing what we might be conducting research for. So I just wanted to underscore that. In terms of the questions that you asked, I think that what we're seeing is, we're really hammering home but droplet ...related to SARS coronavirus in terms of the aerosol transmissibility I think the thing that is going to come out in the future. And we're really going to look at is that we've traditionally looked at droplet and aerosol into discrete categories where you've got kind of the measles based aerosol transmission, which is highly transmissible that those infectious particles can be carried vast distances on very small particles for a long period of time. And I think what we're going to start seeing, there's a growing body of evidence that this is more a spectrum as opposed to two discrete categories. Where different diseases like influenza and coronaviruses probably fall somewhere in between a firm droplet transmissibility and the measles based aerosol transmission. And that there's a continuum there based off of particle distributions and concentration of pathogen in those various particle sizes so I think that moving forward, this is going to be a significant area of focus in terms of protecting our health care workers. And you know this is anecdotal. And I think something that that we need more evidence on but I think the evidence that's coming out with the RNA being carried ...That were one we're going to look for those infectious ... virus particles, but I think it's supporting this notion that for sustained regular close contact right that that is going to increase the likelihood of an aerosol transmission events of those individuals that have sustained close contact in that space. Whether it be within six feet or outside the 6 feet, but that we're getting back to them infectious dose principle in terms of what is it we really don't know. Is there sufficient infectious virus in very small particles to infect someone? Or is it repeat exposure to multiple particles of a small size that's going to bear the risk? I think those are complex studies that are difficult to carry out in the, in the operational environment. But I think we'll see much more evidence coming forward in the future.

01:25:04.470 --> 01:25:23.820
Dr. Hamburg: Thank you. And there I know it's not your area of specific focus, but a lot of questions about seasonality since you've worked a lot with Singapore where they've obviously had cases and it's hot. I don't know if that's enough to give us insights, but in your work, have you been able to develop, you know, some evidence that would be useful as we think about whether to expect to see seasonal

variations with this novel coronavirus?

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01:25:39.180 --> 01:26:36.060
Dr. Lowe: Yeah, so a lot of modeling and projections around that that topic. And I think the best models and projections that I've seen related to that do tend to indicate with raising temperatures, there's likely to be lower transmission. But then on the flip side, higher levels of humidity tend to counteract that trend. So I think there's not really good data to definitively say that that necessarily humidity or temperature really impact transmission, it's probably going to be more driven by behaviors of people of humans in different environments. That is, in cold environments we tend to stay indoors and closed confined spaces and have greater human to human contact. Whereas when it's warmer more people are outside and greater distances. Really hard to unpack all of that. But the models seem to say higher temperatures lower transmission, but that may be counteracted by higher humidity.

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01:26:37.680 --> 01:27:23.430
Dr. Hamburg: Well, thank you. And one last question is going to go to you, Dr. Lowe, because I think we're going to have a chance in a later webinar to circle back to some of these drug treatment issues, but we want to take advantage of your expertise right now. A question about ozone and UV light for killing the virus, should we be integrating that into some of our health care management settings? Is that something to think about as a protective measure in in high density gathering sites going forward? If we're going to be living with this virus over time. And how, how do you think is the best method for us to be thinking about sanitizing overall?

01:27:24.360 -->01:28:44.250
Dr. Lowe: Um, yeah, so great question. I think cleaning in general is as we've shown in our partners in Singapore displayed is incredibly effective for the SARS coronavirus too. We saw widespread use of UV in China to disinfect things like buses and really large complex spaces that can take a long time to manually disinfect, so there's promise there. In terms of ozone. Ozone can be used more as kind of a, an air cleaning agent. But its efficacy for whole room decontamination is complex. It introduces a different range of occupational exposure risks for that for health care workers in that it's a it's a noxious gas. You have to contain it in that space at a high enough concentration to activate viruses to of course bears risks to providers that are in that space. And strong evidence for use of UV light and vaporize hydrogen peroxide for whole room disinfection especially in hospitals and in different environments generally has lower occupational exposure hazards that comes with it as opposed to a true gas and both of these are used in quite a few hospitals already

as a tertiary or terminal option after you've done manual cleaning to go in and do a much more broad disinfection stuff.

01:28:46.200 --> 01:31:03.000
Dr. Hamburg: Well, thank you so much. It's clear that we could spend a lot more time discussing these issues and that our speakers have a breadth and depth of knowledge that could enlighten us all. But this does really need to conclude our webinar for today. Our next webinar will take place next Wednesday, April 15 at 5 pm Eastern Standard Time. And it will focus on crisis standards of care. everyone registered for this webinar will receive an invitation to the next one. I do want to say to all the people whose questions were not asked and answered during this webinar that a frequently asked questions sheet will be being developed in response to those questions, to respond to the sort of different broad categories of questions that have arisen so monitor the webinar. Also I want to remind you that this webinar has been recorded the recording, a transcript and slide presentations will be available on covid19conversations.org.

So let me just extend the deepest thanks to our panelists; great presentations, great discussion. I wish wish that we could have continued on, but time doesn't allow. Let me also thank APHA and the National Academy of Medicine for sponsoring this webinar series. And thanks to all of you listeners for joining us today, for supporting this new modality for doing these kinds of panels, but I think it worked. I was a little skeptical, but I think that we're finding new ways of talking about really important issues and coming together as a scientific community and the public to be able to ask and answer, a set of critical questions for our own health, the health of our communities and ultimately our nation and the globe. So thank you all. Best wishes for your health and safety. Take care. And we are now adjourned. Thank you so much.