

WEBINAR TRANSCRIPT

Pandemic Vaccine Development and Lessons for COVID-19

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Mitchell Warren: I'm delighted to welcome everyone here to this webinar looking at pandemic vaccine development, somewhat historically, as well as most importantly, lessons for COVID-19.

We're also going to have a chance to look at some of the therapeutic research, knowing that Helen Rees is going to be joining us hopefully very shortly from South Africa as well. And we now have several hundred of you on the line. We also got a lot of questions in advance of the call that we'll be going through. You can also email AVAC at AVAC.org if you're having trouble with the Zoom feature.

We did have a webinar just last week with Carl Dieffenbach from the NIH and Yvette Raphael from APHA in South Africa and Lillian Mworeko from ICW East Africa. A recording of that call, which looked also at the HIV COVID interactions, and information that was accurate at that time, is online and that link is available at the AVAC Web site, as will be the recording of this call. And we're really grateful to have everyone here.

I do want to say just before we kick off, whether you knew her or not, the link between HIV research coronavirus became more real than any of us might have imagined, and more real than any of us ever hoped it would be, in the very tragic news earlier this week that Gita Ramjee passed away.

Gita was a dear friend and colleague to so many of us on this call and any of us working in HIV prevention research. To lose a leading light in this field, an inspiring colleague and friend to so many of us is always hard, and to know that it happened in the midst of and because of the coronavirus really brings home the importance of our collective work, whether we work in one epidemic or many.

We have to keep... her approach. I think that she taught us all that in the face of often disappointing research results, you had to get back and do more. And that was certainly the lesson, I think any of us who knew her in the microbicide, and larger HIV prevention field, knew over decades of her leadership. And just wanted to acknowledge that at the top of this call and maybe take just a moment before we move into the content together. All right. Again, apologies for having to start that way, but I can't imagine not.

But we did really want to bridge from what has happened for now almost 40 years in HIV research and in other pandemic vaccine developments to look at what the state of the science is in the current environment. And we couldn't

think of anyone better to have that conversation than Mark Feinberg. For the last several years he's led IAVI and doing remarkable work both in HIV vaccine development as well as in other areas of vaccine development. But as many of you may know, before that, he had a long career at Merck, a leading pharmaceutical company, and worked on a number of interventions and most particularly the Ebola vaccine.

But Mark has broad experience not only in the pharmaceutical industry at IAVI, but previously at Emory University and understands academic research, and early on was also at the NIH, the Office of AIDS Research. So [he] really brings the public and private perspectives together. And delighted to have you here to explore the historic lessons from other vaccines that have been developed, and what we might expect in the future for coronavirus.

Mark Feinberg: Thanks very much, Mitchell, and I just want to echo your comments about the loss of Gita. I mean, clearly I think all of us who knew her recognize what a great personification of the kind of humanity, compassion, science, focus and commitment to public health that the world needs so much these days. And [she] was a friend, an inspiration to many of us. And as Mitchell indicated, it is a profound reminder of the global impact of the SARS-CoV-2 pandemic and how it's going to touch so many people's lives around the world. And, you know, clearly the loss of a beloved member of our community makes that even more real.

As Mitchell indicated, I've been asked to talk about how my experiences in HIV vaccine development and the Ebola vaccine development might be useful in promoting a broader understanding of what will be necessary to expedite the development and availability of an affordable, efficacious vaccine against SARS-CoV. And how can we make that globally accessible in a way that has the desired impact to protect people all around the world, regardless of the country or the circumstance they are living in to be protected against this awful disease.

I have also been asked to address how new partnership models are needed to meet such an unprecedented challenge that we're facing now in trying to develop a vaccine against SARS-CoV-2 to as quickly as possible. You know, clearly, I think there are valuable lessons from the past. But what we're facing now is truly unprecedented. And I'll talk a bit about that. And I'm sure that will come up in questions that arise later in the discussion.

My background in HIV, as Mitchell indicated, is fairly longstanding. I've been working on the virus, in terms of studying its pathogenesis and prevention, for as long as we've actually known of HIV as an isolated virus. And I did play a role in the development of the Ebola vaccine while I was at Merck, as Mitchell indicated. And also in light of that, and I'll talk a little bit about this, played an important early role in the efforts to work with multiple stakeholders to try to be better prepared for future outbreaks. And that gave rise to the formation of

what's now known as the Coalition for Epidemic Preparedness Innovations, or CEPI. And when we're thinking about what we've learned from the past, and how we can build upon those lessons and do even better today, I know there are a number of questions that people have as we consider the global response to COVID-19.

First, how do we do our best to ensure that SARS-CoV-2 infection does not become an endemic infection that plagues humanity for many years to come? Clearly, all of us recognize how that can happen, and HIV is certainly the most vivid and impactful example of an emerging zoonotic infection that gets a foothold in the human population and you just have such a struggle to get rid of it.

Secondly, what role can a vaccine play in controlling and potentially eradicating the COVID-19 pandemic? Thirdly, what are the prospects for developing a safe and efficacious vaccine? And when can we expect that one or more of them will be available? Given the complexity and urgency of this, you know, the fourth point that I think many people are wondering about is how are different partners working together to accelerate vaccine development and what are the opportunities for that process to be even more effective. And lastly, what more needs to be done to be successful in accelerating vaccine development efforts as quickly as possible.

Given that this audience has a special expertise and interest in HIV prevention, I did want to highlight four specific ways that the response to SARS-CoV, to vaccine development, has been really enabled in tremendous ways by the decades of investment in HIV vaccine research. First off, the tools and insights emerging from HIV vaccine development are now being directly applied to develop a SARS-CoV-2 vaccine and in multi-faceted ways.

One, the techniques of structure-based immune design that have been deployed to make an efficacious or try to make an efficacious HIV vaccine are now being directly applied to SARS-CoV-2. Importantly, tools such as— you know, the efforts that many of you heard about developing monoclonal antibodies for therapy and prophylaxis of COVID 19— these tools were directly derived from the work on HIV broadly neutralizing antibodies.

And additionally, important tools that are accelerating vaccine development such as nucleic acid-based vaccine, such as RNA, DNA, vaccines and viral vectors were really pioneered to a large extent in the pursuit of an HIV vaccine development. So in many ways, we are in a better position to approach COVID-19 vaccine development because of all of the tremendous innovation and investment that's gone into HIV vaccine development.

Secondly, and I think everyone on the call really appreciates this, HIV certainly put equitable global access front and center in the discussions of any development of any biomedical innovation. Not only do we need to think about how to expedite the development of an efficacious vaccine, but we

need to figure out, right now, how to make sure that it's available to everyone who needs it, regardless of their geographic or economic circumstances.

Thirdly, I think the investment in strengthening local research capacity, and efforts around community engagement that were put in place to support HIV research and development and treatment programs is now enabling many countries, including low-income countries, to have a stronger foundation to support the local response to COVID-19. And that not only includes expediting the availability of testing for the virus, but also engagement, in meaningful ways, in vaccine and therapeutic research and development.

And lastly, the point that I would make is that one of the things we all know that HIV has done, in the global response to it, is it gives you reason to believe that what was previously considered impossible is actually possible. I think what many of us will remember when antiretroviral therapy was first developed, people thought that it would be impossible to make it available in resource-limited settings. And we all know that that was not true. And the emergence of really important partnerships and significant investment by governments in organizations like PEPFAR and the Global Fund, I think set a meaningful precedent that puts us in a better position now.

Reflecting back on the lessons from Ebola—turning to that now, and as Mitchell indicated, I coordinated that program while at Merck from the early days of the vaccine engagement effort through the time when an efficacy result was obtained in the study in Guinea. That happened with an unprecedented pace going from a first-in-human study to an efficacy result in approximately 10 month period of time. So that certainly set the sort of speed record for development of a vaccine.

And I want to just emphasize that there are a couple similarities between that experience, as well as some differences [to COVID-19]. With respect to the similarities, it's clear, number one, that there's going to be a need for multi-sector partnerships, including among many organizations that may not have previously worked together and may have even had some degree of tension and hostility between them. And that's certainly what happened with Ebola. It brought together a number of organizations to work together very effectively who previously had not done so. And that was really critical for the success of that effort.

These kind of multi-sector partnerships are very complicated to navigate, but they can be very effective and there really isn't going to be any alternative if we're going to expedite the development of a COVID-19 vaccine. And I think we have some additional tools and opportunities here, but it's clear that we're going to need new ones as well.

The second similarity is that it's far better to be proactive rather than reactive. And one of the impacts of the response to the 2014 to 2016 Ebola outbreak

was really changing how we think about preparedness to address emerging infectious disease threats, including what's been referred to as pathogen X, the newly emerging viral infection which the SARS-CoV-2 fits very well.

And this is what stimulated the formation of the Coalition for Epidemic Preparedness Innovations, which is an amazingly important organization that includes funding from multiple public sector entities, governments and organizations like the Wellcome Trust and the Gates Foundation. CEPI is now directly involved in supporting vaccine development against SARS-CoV. And Helen Rees is currently the chair that the CEPI Scientific Advisory Board. So she may talk more about this later. That was a role that I had previously played in the early days of CEPI.

What's very different, though, between Ebola vaccine development and SARS-CoV-2 vaccine development is, number one: the Merck vaccine, now known as Ervebo, it didn't start from scratch with the emergence of the 2014 to 2016 outbreak. That vaccine had been worked on for almost a decade preceding the 2014 outbreak. And there was a lot of preclinical data on that, including efficacy and some safety data in pre-clinical settings. And a vaccine had already been GMP [Good Manufacturing Practices] manufactured and was able to enter the clinic almost immediately when that outbreak emerged.

Secondly, the outbreak was largely geographically contained in West Africa, primarily in Liberia, Sierra Leone and Guinea, which is very different from the current global reach of SARS-CoV-2. Thirdly, a smaller number of vaccine doses were needed to address that outbreak. That could really be handled by one entity alone, in this case one manufacturer would be sufficient to meet the global need. And the fourth one is that the outbreak was waning as vaccine development proceeded. So it was really a race to demonstrate vaccine efficacy against a decreasing incidence infection rate. And while it's not clear what's going to happen with COVID-19, it's quite likely the virus will still be widely circulating when vaccines are ready to enter efficacy evaluation.

So as I conclude my comments, I just wanted to make a couple of points that maybe will be helpful for those subsequent discussions. First off, many people are hearing the statement that a vaccine will be available in 12 to 18 months. And I think it's really important for all of us to ask what are people really meaning when they say that? Do they mean that we'll have efficacy data on one or more vaccine candidate, or that adequate global supply of an efficacious vaccine will be available and being actively implemented to stop the pandemic... This is especially important because unlike Ebola, where you might need a few hundred thousand doses, we're going to need billions of doses of vaccine most likely. And this is a huge difference. And I think everyone is focusing attention on how fast the initial vaccine candidates, including RNA vaccines, have gone from recognition of the pathogen to entering the clinic, including these novel nucleic acid technologies. But is it

really the most important criteria about being fastest to the clinic or fastest to global access? You know, what needs to be done?

How are we going to scale things up? These are all very important. How are the vaccines going to be delivered to all at risk populations or multiple immunizations needed? Do we have the requisite delivery tools? I think we're seeing this in the case of HIV testing, that it's not just the test kits, it's the supporting materials. And if we're talking about a vaccine that's administered intramuscular, we will need adequate numbers of needles, syringes or specialized delivery devices in the case of some of the DNA vaccine.

So when we're thinking about the development of a SARS-CoV-2 vaccine, I think it's important to note what is truly unprecedented about it. Number one, the urgency to develop it. Number two, that we're really starting from scratch with a newly emerging previously unknown pathogen. Number three, I think we don't really know what the regulatory framework is going to be that expedites vaccine development while ensuring scientific rigor and volunteer safety. And what will be the framework for widespread introduction of a vaccine before a formal regulatory approval might be available. For the magnitude of the need is really unprecedented, as I mentioned before, and we'll likely need billions of doses. And there's no way that any one company or developer can meet this need by themselves. And clearly new partnership models are going to be needed to address that. And what's going to be really important.

Fifthly, governments and donors are going to need to make investments now at risk if we're going to be able to expedite actual impact. We simply cannot wait until we have efficacy data before we begin manufacturing scale-up. And I think it's really important, lastly, that we focus on the need for equitable global distribution and how these decisions are going to be made, because it's quite likely that, at least initially, limited vaccine supply is going to be available. And how do we do this in a world where nationalism seems to be the predominant political force these days? So I think there's a key role for advocacy here. There's a key role for focus on equity and affordable access. And I know those are all things that many of you are intimately familiar with and you have an important role to play here as well. So I'll stop here and be happy to entertain any questions you have.

Mitchell Warren: Fantastic. Mark, that was a superb overview of where we are and clearly where we need to go. I do want to let people know that your questions and comments coming in are fantastic and they're being added to the queue. I know a number of people asked about slides and neither Mark nor Helen have slides. A recording of this call will be made available and undoubtedly we'll all together make some key factsheets coming out of the terrific inputs that Mark just provided. But just wanted to let people know, you can still use the Q&A feature in the chat feature on Zoom and email AVAC at AVAC.org. But before we open it up to questions and conversation, I want to turn to

Helen Rees. Helen, I know a little technical difficulty getting you on. I hope you're there. Let me first check to see if you're there and then I'll actually introduce you.

Helen Rees: Yes, I'm here. Can you hear me?

Mitchell Warren: Yes. Loudly and clearly, Helen. Thank you so much. I think most people on this call will know Helen. As Mark just alluded to this, Helen is currently the chair of the Scientific Advisory Committee of CEPI that is driving forward a range of vaccine developments and she can certainly speak to that. But as all of you will know, Helen wears many, many hats and for a very long time served as the chair of the scientific advisory group of experts SAGE at WHO. Looking at all vaccines. So has a lot of experience on the vaccine front. In addition, Helen is quite involved in emerging trials right now in South Africa around therapies, treatments for COVID-19. And so we have a chance to engage with that as well. So perhaps I'll turn it over to you, Helen, to provide some comments on both those fronts, CEPI and vaccines, as well as the treatment research. And then we'll open it up to a conversation. es, I'm here. Can you hear me?

Helen Rees: Thank you very much. Good afternoon. Good morning. Good evening to everybody. And I'm going to talk a little bit about CEPI, building on what Mark has said. And then perhaps, then a little bit about the other trials and thinking that's going on. So CEPI was established after the Ebola outbreak in West Africa and the aim was to accelerate the development of vaccines against emerging infectious diseases, but also to enable equitable access to these vaccines for affected populations during outbreak. So the focus is broadly: Preparedness—so that the CEPI has been thinking since its founding about what are the priority pathogens we need to think about...an interest in the MERS, CoV was one of those pathogens that was identified; [Investment—] starting to invest money already in those candidates; Response to accelerate the research—so that in the event of an outbreak you can move extremely quickly; And sustainability—so looking for durable solutions.

And this really was because, as Mark said, there was a scramble in response to the Ebola outbreak with quite a number of candidate vaccines, but a lack of global coordination. We got one phase III trial, which has been extraordinarily important in the Ebola vaccine. But one of the things that CEPI has always had on its agenda, as a backdrop to this, is what you heard Mike describe as disease X. So this is a disease that everyone has been fearing, likely to be the kind of disease we're now seeing, that jumps from animals to humans. And most likely, as everyone had predicted, to be a respiratory disease that would spread extremely rapidly around the world because of air traffic and the movement of people and to have a significant mortality. If you remember, we had pandemic flu some years ago.

We were equally worried. But the death rates associated with that was much lower than we're currently seeing with COVID-19. So in January of this year,

the scientific advisory committee of CEPI actually met because this new virus had been identified. And I remember that call very clearly because we were saying do we asked the board of CEPI to release a lot of funding looking for candidate vaccine for this new virus. And we said at the time, this was before there was human to human transmission... So what we had seen at that time when we had that call was animal to human transmission. And the comment made, I remember, was I think we should release this money and we should back candidate vaccine development now because, at the very least, we can regard this as a dry run for disease X. But at the worst, this is going to turn out to be disease X. And indeed, of course, it is the disease X that we've all feared.

So, the way that CEPI works is that there was a call for proposals. People submit and there were nearly 50 submissions. And then the Scientific Advisory Committee, together with external experts evaluate and score very objectively the application. So CEPI is supporting the development of eight different vaccines, which have different what are called "platforms" and somewhat different antigens. Mostly the antigens for this virus are the same. And they're somewhat different stages of development. But we didn't start anything that was too high up the development pipeline, too far away from getting into the clinic, as Mark said. So we looked at things that were looking promising, things that looked promising for the original size outbreak for MERS. Platforms that looked like we could rapidly adapt them for COVID-19.

As a result, there are currently eight products that are in development, but there are many other parties also looking and supporting vaccines. And they're between 40 and 50 candidate vaccines worldwide now being looked at from places like NIH, but also in China as well. And China's vaccine development has grown in leaps and bounds in the last 10 years. So lots of vaccines. We've had the first clinical trial in humans and we're pushing, as you heard, as fast as can be. I think with that number of vaccines and looking at the potential of these vaccines and also looking at some of the early data around some vaccine candidates for MERS and SARS, and I think that we will get vaccines. But if we have 40 to 50 candidates now, I think we will recognize that most of those are not going to pass even the first post. So if we can get two, three vaccines from this, I think we would be thrilled. And so that's the aim.

And the other thing, of course, is having to be looked at now is not only what the vaccine is, but also when choosing these candidates, how easy is this vaccine to manufacture? Are there manufacturing sites that are going to be easy to convert? How quick is it going to be to produce these millions and millions of doses that we're going to need? And who's going to invest that money at risk in manufacturing now—because as we heard with the epidemiology of COVID-19, in countries, we're seeing that not only the second wave, but I think we all anticipate that in many settings this might well become endemic or even seasonal. So this is going to be a nasty virus that

we're going to have to deal with for some years to come. Perhaps in a different context, than the one that many of us are sitting in now. I'll stop there. Oh, no, I won't. Because you wanted me to tell you briefly about the other trials that are going on worldwide. Mitchell, shall I continue?

Mitchell Warren: Yes, I think so. It would be great Helen.

Helen Rees: OK. So the other thing in response to COVID-19 was—and clearly China was trying to do this as it sort of came to terms so quickly with this outbreak—was what other things do we need? And clearly, very urgently, we needed effective therapy. We have therapies that would alleviate symptoms, say paracetamol for mild symptoms and things like this, oxygen for respiratory distress. But we have no at the moment, we have no therapies that have been shown definitively to change the course of the disease. So we wanted therapies and we needed to find out if they work.

But just like HIV, we also want to find drug interventions while we're looking for a vaccine, [that] will also protect risk populations. And in particular, at the moment, people are extremely worried about the health worker and their workforce, because if we cannot keep them at work, the outcome for patients is going to be much much worse. So in addition to the vaccine work there, WHO gathered together some of the world's best experts to look at the existing drugs and the emerging drugs to say, can we repurpose existing drugs? And can they be used for COVID-19? Is there any indication that these might be successful? And also, are there any drugs that are in the early stage of development? They exist, but they're in the early stage of development that might have utility in shifting a COVID-19 patient. And one of the things they looked at was, what did we learn from the MERS outbreak with their products there that we used, or the SARS outbreak? And what were the products that showed potential? And from all of that, WHO Identified four different products.

And there's now a global study that's underway called Solidarity. About 60 to 70 countries have indicated interest in joining it, and about ten countries so far are already implementing this protocol. And those include many European countries, but [also] some countries from the Far East...and South Africa, in terms of the African region, this is a country that's quite far advanced in doing all that's required to set up our hospitals to be able to participate in this trial. The other thing that's being looked at, and there are two big studies looking at this, are drugs for protecting particularly health care workers. And there are big studies that are exploring whether it's possible with existing drugs to either prevent infection or change the course of disease and prevent deaths. And also, what would be the least dose of a drug that would be able to do that? Because this is prevention, and as you know, with prevention we want drugs that give fewer side effects and that are easy to take. So I'll stop there for now. Thank you.

Mitchell Warren: Great, Helen. Thank you so much.

And both you and Mark providing terrific overviews and generating lots of fantastic questions. I'm going to try to bundle a bunch together and happy to have both of you respond as best we can, and we'll get us as far as we can in this fantastic list. I think, you know, both of you touched on the incredible urgency and of the dynamism with so many candidates in the vaccine pipeline already in such a short period of time. And you talked about the coordination, and particularly CEPI's role in that.

But a number of questions came in about the selection of which candidates go forward. How does that get decided? Is that CEPI alone? And what are some of the basis for those decisions, given the issues you both raised in terms of the need for manufacturing? So what are the tradeoffs? How does that global coordination happen? What more needs to happen? And related to that, a question specifically, Mark, for you— you describe really nicely the Ebola experience and partnerships coming together amongst groups that don't always work together or hadn't worked together in the past. And so a question there about how to manage those partnerships and even the competition amongst developers. So I wonder if you both might look a bit at those issues related to coordination and product selection and prioritization.

Mark Feinberg: Would you like to start? Helen?

Helen Rees: Sure. So you obviously have to have objective criteria and when you are looking at the application. So some of the criteria were: First of all, how far advanced down the development pathway were the products? So if somebody had a brilliant idea, but it was still very, very far back in the laboratory, that's not really going to do too well. It wasn't part of what was required at this point.

Secondly, is the technology that's being used a licensed technology, or is this novel technology? Now, both have a place. The advantage of license technology is that they would have been proven to have worked for other vaccines. So platforms which have worked for other vaccines...Where you can, if you like, take an antigen and plunk it onto a platform which is already proven. But on the other hand, there might well be a place for novel vaccine, particularly because this is a novel virus. We need to have a range of things, so that we press the right button and find out what works.

Thirdly, how quickly can you go? Because if people are saying, well, we think we can get this far in two years, that's not as good as the people who say, we think we can get into the clinic earlier. We think we can do this by then. So speed was one of the other things.

Manufacturing scalability, and Mark can talk more to this because he's the real expert, but some technologies, the vaccines are much easier and some are much more difficult to manufacture. So if you choose something that's

going to be extremely difficult to manufacture, or it takes a long time to manufacture or it takes a lot of work to manufacture relatively small numbers of doses, that is also potentially you're going to be a disadvantage because as you say, at the end of this, we want to be able to churn out millions of vaccines. And then looking at all of this together, looking at who the applicant is, what their experience is, are they linked to manufacturers, have they done things before. Putting it together, what is the likelihood of success? Those are some of the considerations.

Mark Feinberg: Thanks, Helen. I would just second everything that Helen said. With respect to the sort of bigger picture question that was asked about how this is all coordinated and how decisions are made in a strategic way, and it's not a competition... but there's a shared community response to this, that is actually something being built as we speak. When we talked before about the importance of being, you know, prepared rather than responding, I think innovations like CEPI have been really important.

But in some ways, this disease emerged before we actually had a real global governance mechanism in place. And that, I think we will, unfortunately, have to address. But I do think if one positive thing comes out of the COVID-19 response, it will be to clarify the importance of having proactively defined models of collaboration, evaluation, decision-making and willingness to make investments at risk so that one can go as quickly as possible.

Mark Feinberg: I wish I could say that there actually was a mechanism in place that would allow that kind of equitable access, shared decision-making, prioritization, and everyone working together—that's not in place now. I think there are lots of goodwill and lots of people who want to make that happen. But I don't know that it's going to be easy. But the extent to which we can do that is going to be critical.

And with respect to the partnership question, the way I often talk about things is there's a science of innovation, which really drives the actual development of the vaccine... but there's this science of partnerships, which is an area that needs additional attention because it is something that requires thoughtfulness and new strategies. And we need to study that better and get even better at that. And I hope that we'll be good enough to respond quickly to this pandemic. But I know that this pandemic will force us to become increasingly good at it for the future.

Mitchell Warren: Beautiful point, Mark, about the science of partnerships and needing to focus on that. I wonder, you both touched on looking forward and in the magnitude of need, and some of these delivery challenges. I wonder if you might both pick up on it. I'm thinking particularly about... delivering a vaccine to adults is less well known to us than classic EPI vaccination programs. And I wonder if you might both think ahead to some of the challenges, but also what, if anything, should we be doing now, as we see these vaccines in development?... To think anew about how to address some of those delivery challenges and what will undoubtedly be this huge magnitude of need?

Mark Feinberg: That's a really critically important question. And there, too. I think we unfortunately are starting from scratch as people have a better understanding of this pandemic and its global reach. and the kind of issues that need attention immediately. There is an effort to try to stimulate that dialog. I think it is not sufficiently well developed and it needs much more focus and attention.

I mean in some ways, I think we will have to go back to earlier examples. Everyone knows the disease that was eradicated from human populations was smallpox, and that was eradicated through a focused strategy that involved delivery of a vaccine to large numbers of individuals around the world with targeted vaccination strategies where appropriate. But it also was made possible by a simple delivery tool, the bifurcated needle and a single dose administration and an inexpensive vaccine. We may actually find some useful lessons in going back and reading that history. But we definitely need to put in place implementation programs now, just like we need to put in place manufacturing programs now.

Mitchell Warren: On that manufacturing question... You did, Mark, help us all realize that this is a vaccine inevitably for everybody. How do you manufacture to that?

Mark Feinberg: Well, I mean, I think that's a very important question. So one issue to recognize is that there's limited vaccine manufacturing capacity globally and it's very rare to have any excess capacity. And many vaccine manufacturing plants are dedicated to a specific vaccine and they can't be readily adapted to produce another vaccine. And it's not like many vaccine developers are going to totally redirect their manufacturing to make a COVID vaccine. You know, there are efforts to try to look at the global landscape of available vaccine manufacturing capacity.

But going back to Helen's point that different vaccines being developed often use different manufacturing strategies, and that's not really optimal. I think we need to understand how can we have some harmonization so that all these classes of vaccines might have common manufacturing platforms, which would involve coordination and communication early in the development process. And I think there's awareness that needs to happen.

And CEPI and others are trying to address that issue. But it's really important that we make progress on it. But, you know, the need to produce billions of doses is something that is unprecedented in the timeframe we're talking about. And I think that's going to require multiple vaccine manufacturers to work together to meet that global need, and build upon and take advantage of existing technologies for production, rather than novel ones, which might have problems with scaling up. So that effort really is under active exploration. But like so many other things, it needs to be taken to a much greater scale than is currently taking place. This is an unprecedented challenge.

I believe that it can be solved, but it's going to require totally new partnerships, including partnerships between private sector companies that often may not have the opportunity to collaborate or are precluded by things like anti-trust mechanisms from collaborating in this way. A lot of that has to go out the window and new models need to be developed.

Mitchell Warren: Sorry, Helen, I cut you off, but about all of this too... please feel free.

Helen Rees: Well, I'll start off with the issue about the need for vaccine manufacturers. And just to say, I mean, the global world order, as we all know, is going to be reshaped. Now developing country manufacturers, they've really come into their own. In recent years we've seen, for example, India has become a powerhouse of vaccine manufacture. And China is also really growing in its ability. And there are other countries particularly in the far east, but other countries who are aspirational. So Egypt, South Africa, etc.

The second thing is that there was a meeting of health ministers about two or three years ago now, in Addis [Ababa]. And these are all of the African Union health ministers and finance ministers. And they came out with a declaration around vaccines and they all said we want to be able to produce our own vaccines in the African region. So I think that's not going to solve the problem now for quick manufacture. And we're going to have to look at really well-established manufacturers who can scale up. And we probably will see, you know, not only groups like the Indian manufacturers, but also China, which will come to the forefront. But in the future, in the medium to longer term, I think that this is an opportunity for developing country manufacturers.

But I just wanted to come back to your question about how do you give a vaccine to adults. So just two thoughts on this. It's a very good question, because where have we massively failed in giving vaccines to adults: seasonal flu. You always have to beg people, until now, until COVID, to have a seasonal flu jab. Now, of course, with winter coming in the southern hemisphere, people are dying to get the seasonal flu jab because they recognize that co-morbidities, the two viruses which occurred in China not infrequently would be very bad news. But people don't take up seasonal flu. You're quite right. And you can beg and plead and people don't—not even people who are at risk. On the other hand, we have the experience in the African region of a vaccine that was developed specifically for what's called the meningitis belt, which is a belt across the central mid African countries.

And then, for meningitis A, which was a major killer and came in outbreak almost every year, the vaccine the WHO supported called MenAfriVac was developed. And they were giving it to people up to thirty years of age and the queue went round the block for that because people were so scared of meningitis. And so I think if we were to have, today, a vaccine, the queue would be so long. I mean, people would march with their feet. They would want everyone in their families, children, the elderly vaccinated. Assuming we

get the vaccine, and I'm fairly confident that we will, we're also, are we going to have to then give it to the first priority people? Who would they be? Well, at the moment, as I said, it would be health care workers. But it would also be those people that we've seen most vulnerable to this infection, which includes large time, the elderly. That begs another question about the elderly immune system.

Would a vaccine that works well in a 20-year-old work well in a much older person because their immune system, just like other parts of the body, it's not as strong as it used to be. So if you get a vaccine, it's not going to respond in the same way. So there are many questions about the vaccine and who do we give it to, given that we will have limited supply of.

Mitchell Warren: Helen, that raises so many important issues of ethics and equity, and both of you have touched on. So just. And also the issue of the trial design itself. Just thinking about how these trials will be done and then how one knows both for older people and for younger people whether they will work. And I'm sure many of you are also aware that we're getting near the top of the hour. We're not going to get to every question. And but we will be following up with Mark and Helen. And obviously there are many more conversations to be had.

I do want to ask one very specific question that came in for you, Helen. Because a lot of people were curious about the Solidarity trial and what those four arms of that trial are. And I know that's available online, I think might be helpful for this group to hear what those four arms are. But also a question both for that trial, but also I think for all of this work, both for treatment and for vaccines, one that I know both you and Mark think a lot about in our own collaboration.

And that is: how does community engagement happen? How can it happen? How should it happen in a pandemic situation, keeping communities involved in the research itself? And obviously, then we get to the access issue. So I wonder do you want to quickly talk about the four arms and how engagements happening. And then maybe, both of you, think a bit about how we might rethink or re-energize engagement around it.

Helen Rees: So thank you there. Well, there are four arms which have an additional product. But there are five arms in the study altogether. The first is standard of care, which is defined... As I said, there are already more than ten countries participating and soon there'll be many more. So the standard of care is determined by the country, and it's for people who have been admitted to hospital, which means that they must be at least moderately ill. Because obviously people with mild illness will remain in communities. So the standard of care is the first arm and standard of care applies to all of the five arms.

The drugs that are being tested are lamivudine ritonavir. Then lamivudine

ritonavir with interferon beta and then remdesivir, and chloroquine or hydrochloroquin. So they good the arms that are being looked at. And as I say, WHO has an expert panel, really the world's expert on all of these things, looking at what we know about the virus and what we're seeing all the time, because people are obviously trying out new therapies on a small scale all the time, and reporting things. So there's continuous review of data, and other extra products we should be adding, and the trialists decide that you can add extra arms with new product. But also, in the event sufficient patients are enrolled, if any of these products are shown not to be effective, then they will be dropped from the study.

And from the point of view of a community, I know we're coming quickly to the end, I think that we have learned... A lot of people are saying this: the lessons from HIV that we're able now to take into our response for COVID-19 are extraordinary. Community is one of them. Communication is another. Avoiding stigma is another.

Partnership in trials, especially when we get to big vaccine trials, will be another. Information sharing in the accuracy of information, not allowing people with counterfeit or rubbish cures to be marketing that and exploiting people [with the false promise of] cures and test kits and just about everything else.

Today I heard that in one of our townships in South Africa, somebody is administering a vaccine from a major grocery store. So these are the kinds of things where the community is absolutely critical and we've learned so much from HIV. And I think we're already seeing that we're able to transfer this into our response to COVID-19 in the countries that have had HIV experience.

Mark Feinberg: As always, I completely agree with Helen. I would just want to reflect, additionally, when we're talking about community here, we're really talking about everyone. We're talking about everyone on the phone. We're talking about all of our families. We're talking about all the people in the countries we live. You know, we're talking about people at risk. We're talking about infected people. We're talking about responders.

You know, it's really, I think, going to be very evident where leadership comes from in this response. And while we all hope that governments will take a strong, decisive leadership role, I think it's quite likely, as we're already seeing, that the most effective response is going to be from the ground up. And that really involves people at risk who are affected, who are stepping forward to try to solve this threat.

Mitchell Warren: Thank you so much. I will just say from an AVAC perspective, both that we've had the great pleasure of working with both IAVI and Mark and WITS Reproductive Health and HIV Institute with Helen, and with many of you on

the line and with UNAIDS in the good participatory practice guidelines which have been created in HIV, adapted for TB vaccine and drug development, and for emerging pathogen research... And clearly a need to collaborate together on that for this.

Obviously, many, many additional questions. There was a question, I think actually very importantly for a lot of us who work in HIV vaccine advocacy and science, that is related. We'd love to have you both talk about, and that is we spent a lot of our time in HIV talking about HIV subtypes, about the potential for mutations. We've obviously seen past vaccine candidates in HIV potentially modify or even accentuate risk. How does that all get considered in thinking through the range of COVID-19 vaccine candidates? Are those real issues and how do those get addressed?

Mark Feinberg: Well, it's an important consideration always when one is developing a vaccine. You know, fortunately in this case, the replication mechanisms of coronaviruses are more accurate than those of HIV. So genetic variation in the virus is less pronounced and develops less readily. So while we don't yet know for sure all the data about genetic diversity of the SARS-CoV-2, virus circulating around the world do suggest that one vaccine should be able to protect against many viral variants. And we certainly hope that that's the case. We'll have to keep close attention to that issue under any circumstances.

Mitchell Warren: Great. And maybe it also before we end and for both of you, especially given the CEPI experience. We see emergency responses and then sometimes they wane quite a lot. So, you know, we see developments earlier on around a MERS vaccine and then we get past that and it disappears and vaccine development wanes in that area. We're obviously in a very different time and place with COVID-19. But I'd love to hear you both reflect on what we need to be thinking about in the future. Whether this is addressed as a one-off, whether this does become a seasonal issue—thoughts from both of you on how we build for the future so we don't end up in a situation again where pathogen X appears. And you both touched on it, but just thought it might be helpful to have you both opine on that before we close.

Helen Rees: Well, I think the whole idea behind CEPI—and CEPI is one organization and there are many other investments going on—but the whole idea was to think about these pathogens that are a threat, emerging infectious diseases and that are a threat of epidemics and outbreak. So if you look at the kinds of pathogens that CEPI has had selected as priority prior to this: MERS, CoV, Meepo, Rift Valley Fever, Chikugunya, Ebola. And these are all vaccines that really won't have a commercial market. So I think if we've learned anything, the importance here is that we ignore things that don't have a commercial market at our risk because it will come back and bite us. And that's why it's starting to tackle these things that might be quite regional, might be quite

seasonal, might wax and wane, but cause enormous damage, in terms of people's health, mortality and the economy. We can't go away from this, because we've already said this is too important. How many times have we said it now? This is the fourth time in a very short number of years, MERS, SARS, and Ebola and now this. Very few, very few years. And these infectious diseases are causing massive instability either regionally or globally. So these are lessons, I think, that the world will have to hang onto, you know.

Mark Feinberg: And I agree with all of that. I think one thing about this is different is that this isn't an abstract notion. It's affecting everyone's life in ways that are much more concrete and close by the maybe Ebola was, or SARS or MERS, which seemed far away and abstract. This is affecting people in concrete ways. And if something good comes out of this, I hope it will mean that we really get our act together globally, nationally and locally to be better prepared to respond to future risk like this. Because one thing is certain is that this kind of circumstance will repeat itself again and again unless we have a better way of preparing and responding.

Mitchell Warren: Mark and Helen both, I think you've captured it. There's an urgency, a pandemic response, and yet what you both have said multiple times in the hour is the need to do that response while also building something far more sustainable, far more equitable and far more comprehensive than we've ever been able to do. And let us hope that all of that actually it gets done rather than just talked about. There's obviously an enormous amount of work to do. Many questions that didn't get answered.

You also continue to be in your day jobs, leaders in the HIV response, in the HIV research response. And I wonder if there's any last thoughts either you want to put in for... How do we manage a pandemic four months [old] while dealing with the 40-year-old pandemic that really brings many people on this line together over many years. S

Helen Rees: Well, last word I would say is that if ever there had been something that's humbled us all, this particular pandemic is it. It respects nobody. This is therefore a leveler. We speak so much about universal health coverage and SDB [sustainable development goals] about equity. This is going to be something that we're going to have to really look at. And as Mark said at the beginning, we must watch this issue around access. If people close borders and say, mine first and mine second and mine last, and we don't mind about what happens elsewhere, then the world has lost an opportunity to do things fundamentally different in terms of global health and really actually adopting the principles of the sustainable development goals.

Mark Feinberg: No, definitely. I would just clearly we all know that our efforts in HIV have been disrupted by the COVID-19 pandemic. And that means that there is a lost time and lost opportunity. And unfortunately, people are going to suffer as a result. And timelines are going to be delayed. And we collectively need to

figure out how to maintain the priority of the HIV response throughout the COVID pandemic. I do hope, again, being an optimist, that what we learn from the COVID response may also be helpful in the future of the HIV response, just like the HIV response put us in a much better place to address COVID-19.

Mitchell Warren: Beautifully, said Mark and Helen. And the end of the day, I think what I hear loudly and clearly is, is it's about global health. It is not about any one disease over another. And it's not about, as you said, Mark, earlier, and Helen too. And this is not about nationalism. This is global. And if we ever needed to be global health activists and advocates and global health scientists and researchers and global health funders, now is that time. I can't think of two better colleagues, friends and mentors to have than Helen and Mark. We have terrific opportunities, terrific challenges. And importantly, I think to make good on what Mark said, is to give new meaning to the science and the art of partnership, to really move all of this work forward. Really, I want to thank everybody. I know lots of questions unanswered, some requests for additional follow up information. It will all be posted on the Web site with this recording, as well as the recording from last week, the webinar with a number of other colleagues. Find all this on the AVAC Web site. It's avac.org/covid, hopefully super simple, for all of these resources.

We'll be doing additional webinars as needed. If you have information needs, thirsts and hunger's or things you want to offer, please let us know at avac@avac.org and we will do our best. We will undoubtedly be back with Mark and Helen... And many, many others to think about vaccines, therapeutics for COVID as well as in the HIV space and the larger global health space. So, Mark and Helen, thank you all so much. Stay safe and well, all of you on the line. And we look forward to continued work together.

Mark Feinberg: Mitchell, Thanks everyone.

Helen Rees: Thank you very much.