Thank you for the opportunity to be here. It is a great honor for me to address people who have probably been even more stressed than me over this last year. I appreciate what the regulatory people are doing and what making these decisions under this pressure must have been like. So it is my pleasure to be here with you.

I am going to talk about the coronavirus vaccine development, but first I want to talk about some of the ideas we have had about how to be better prepared for future pandemics. This really grows out in part from the Vaccine Research Center itself, which was founded in 2000 to develop an HIV vaccine.

Preparing for and Addressing Vaccine Challenges as Technology Advances

When you think about it, HIV really was an emerging infectious disease. Now it sort of has a life of its own. But this was a regional zoonosis that if it had been found and diagnosed and recognized early on could have been maintained regionally.

Part of the point that I want to make is that, if we can be better organized on a global level, for the zoonotic and vector-borne problems that will arise and continue to arise as they have over these last several years, we could recognize them regionally and contain and control them regionally before they become pandemic problems.

In the past, I think the viruses really have had the advantage over us, because they can adapt faster and have more mechanisms to adapt than we have ever had with our approaches to contact tracing and quarantine. But over time, vaccine development in particular has changed, largely based on new technological advances.

This is a graph plotting out the timeline of new vaccines as they were introduced. This first cluster really came because of the efforts of a few individuals. But this next big cluster came because of the discovery of cell cultures and the ability to grow virus in large quantities to either make live attenuated vaccines or whole inactivated vaccines.
The next group came largely because of advances in molecular biology and the ability to make molecular clones or recombinant proteins or reassortment-type products.

This is where we were a few years ago. But around 2008/2009/2010, a whole new set of tools came onboard, largely driven by so-far-unsuccessful efforts to make an HIV vaccine.

One of those includes structural biology, which I will spend some time talking about today. We thought maybe that the RSV [respiratory syncytial virus] vaccine might be one of the first examples of a structure-based vaccine design that ended up having clinical relevance.
But this other problem, the coronavirus, slipped in, and it may be that it will be the first vaccine based on some of these newer technologies that not only include gene-based delivery but rapid synthesis and manufacturing, and all these other techniques that allow you to really understand the antigenic target and the immune response to that target in much more detail and with much more precision.

Now I think that our technologies maybe have the advantage over the viruses if we apply them. And I think we are in an era where we could apply them in a way that makes this very historically uncertain process of biological development more of an engineering kind of exercise, where we can do things in ways that we could string together a set of predictable approaches that could result in a biological product, driven largely by these technologies.

Technologies, fortunately, are not only things than can make this approach more precise, as I have listed here – the structure-based design and some of the new approaches to protein engineering and self-assembling nanoparticles – but they can make it more rapid. Combining precision and speed is what we need in order to address emerging infectious diseases, many of which we have faced over this last decade.

New Technologies are Transforming Vaccinology

- Structure-based vaccine design
- Single-cell sorting, sequencing, and bioinformatics
  - Rapid isolation of human mAbs
  - Definition of antibody lineages
  - Analysis of immune responses
- Protein engineering of self-assembling nanoparticles
- Rapid DNA synthesis
- Recombinant DNA and genetic engineering technology
  - Rapid cell line development
  - Animal model development
- Nucleic acid and vector-based delivery of vaccine antigen

Taking a More Proactive Approach

After going through the chikungunya and the MERS and the 2014 West African Ebola, and Zika in 2016, we started to step back and say, ‘We really cannot keep doing it in this way forever. We have to take a more proactive approach.’

There have been some interesting papers published by [University of Edinburgh College of Medicine and Veterinary Medicine Professor of Epidemiology Mark Woolhouse] from the UK about the number of accumulating new emerging viruses found in humans, but that the number of viral families involved had sort of leveled off. So it really is, now that they have renamed the bunya viruses, about 26 viral families that are known to infect humans.

I am listing some of them here. These viral families infect humans. For some of these we already have candidate vaccines in humans [see slide #7]. But there are a number of other viral family members behind these that really do not have ready solutions [see slide on next page].

There are a number of virus families where we still do not have a licensed vaccine. I guess I need to move filoviruses from that list now. But there are a number of other virus families, adding up to about 26. And if you add arteriviruses, which I worry a bit about that have not yet been in humans, maybe 27. But there are a number of viral families.
But it is limited. It is a tractable problem. It is a finite problem. If we could address these about 120 known viruses known to infect humans, and then in particular focus on at least 30 prototypes within those, and take those, learn the details of the structures and make monoclonal antibody reagents, understand replication pathways – I am going to be talking mostly about vaccines, but this could also be applied to antivirals and other types of countermeasures – we could establish what I call a ‘prototype pathogen approach to pandemic preparedness’ and have some things, for instance, maybe on the shelf, for at least 30 prototypes, but have other reagents and potential products at least through animal testing for these other 120 known viruses.

In the past, these have been categorized as priorities. But we really think it is important to try to address this in a more systematic way and do all the virus families and sub-families or genuses that might be clustered as a similar package.

So we have envisioned a division of labor between the pathogen specialists who would maybe specialize in an area of: ● envelope viruses with class I fusion proteins ● or viruses with this other entry mechanism, class II fusion proteins ● or another fusion protein entry mechanism ● or non-enveloped viruses – and divide these into four major areas of entry mechanisms for viruses that could be studied in detail by groups of people with pathogen-specific knowledge.

These could be supported by systems and groups…that could perform these core functions more related to development – to combine the research specific for the pathogen and the development with these other functions that could be more core functions.

Viral Families that Infect Humans (no licensed vaccine)

<table>
<thead>
<tr>
<th>Family</th>
<th>Prototype(s)</th>
<th>Other Viruses of Concern</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pneumo</td>
<td>RSV, MPV</td>
<td></td>
</tr>
<tr>
<td>Filo</td>
<td>Ebola, Marburg</td>
<td></td>
</tr>
<tr>
<td>Retro</td>
<td>HIV-1</td>
<td>HTLV-1</td>
</tr>
<tr>
<td>Corona</td>
<td>SARS, MERS</td>
<td>SARS-like viruses in bats</td>
</tr>
<tr>
<td>Parvo</td>
<td>B19, Bocavirus</td>
<td></td>
</tr>
<tr>
<td>Calici</td>
<td>Norovirus</td>
<td></td>
</tr>
<tr>
<td>Polyoma</td>
<td>JC, BK</td>
<td>SV40, Merkel cell virus</td>
</tr>
<tr>
<td>Arena</td>
<td>Lassa, Machupo</td>
<td>Junin virus, Guanarito virus, Chapare virus, Sabia virus, Flexal virus, lymphocytic choriomeningitis virus, Lujo virus</td>
</tr>
<tr>
<td>Bunyavirales</td>
<td>Hanta, Rift Valley</td>
<td>Crimean Congo hemorrhagic fever virus, California encephalitis virus, Batai virus, Bhanja virus, Dobrava-Belgrade virus, Erve virus, Puumala virus, Seoul virus, Tahyna virus, severe fever with thrombocytopenia syndrome virus, La Crosse encephalitis virus, Cache Valley virus, Jamestown Canyon virus, snowshoe hare virus, Heartland virus, Oropouche virus, Andes</td>
</tr>
<tr>
<td>Arteri</td>
<td>Astrovirus</td>
<td>Simian hemorrhagic fever virus (Not yet reported to infect humans)</td>
</tr>
</tbody>
</table>
This is partly how the VRC has been organized. I will briefly introduce you to the Vaccine Research Center, where I work. It was founded in 2000, announced in 1998 by Bill Clinton at Morgan State University. It was established to develop an HIV vaccine, as I mentioned. And even though we do not have an HIV vaccine, these technologies that have been developed to try to make an HIV vaccine have been applied to a number of unmet medical needs and other emerging infectious diseases.

Not only do we have a basic research facility, but we also have: ● process development with a number of engineers that are expert in this arena ● another group of engineers who do GMP manufacturing at a pilot-level scale in Frederick, Maryland ● our own self-contained clinic to test these products, and ● a laboratory that focuses on analysis of these clinical trial samples. It is run by this relatively small group of investigators and program heads and is led by John Mascola, pictured here.

Over the years we have done and delivered vaccines by a number of different approaches, including: ● nucleic acids, which I will talk more about ● vector-based approaches using viral vectors ● one-round vectors ● virus-like particles ● proteins ● nanoparticles, I will mention briefly, and ● monoclonal antibodies.

These experimental products have been shared around the world for different types of diseases. As an example, recently one of those, the antibody, what we call MAb114, was granted approval. This is our first approved product from the VRC. It is now called Ebanga. It is an antibody that was shown in 2018 to treat people with ebola. And it was shown to be efficacious at a pretty high level. So that is an example of what the VRC has done to apply the technologies started through HIV research.
Ebola and Zika Cases and Vaccine Trial Launch Dates

Making these things, as we have learned, is not enough unless you can go fast. We had a vaccine in a vial ready for a phase I trial in 2014 when the West African ebola problem emerged and took the world sort of by surprise.
Despite our best efforts in getting this into a phase III trial within a year, since we had chosen Liberia, by the time that phase III trial was able to start, the epidemic had waned, and we did not get an answer. If you cannot get an answer about efficacy in the field in the middle of an outbreak, then it makes it very hard to invest in these products for the future. So we needed to go faster.

We tried to go faster in 2016, when we started working at the end of 2015 on a Zika vaccine based on a DNA approach. Again, we were able to get into phase III. We got into phase I in a little over 100 days. But phase IIb efficacy in a little over a year. But again, we missed the outbreak and were not able to get a final answer [see slide #13].

So, thinking about how to do this in a faster way: ● looking at platform manufacturing approaches like the mRNA that we will talk about in a few minutes, where you can insert an antigen of choice but use the same manufacturing process, purification process, and release criteria to more rapidly produce a clinical-grade product ● doing more work on prioritization of pathogens ● and again, trying to do this in a systematic way, embracing all the 26 virus families of interest.

**RSV F Glycoprotein Studies**

Our thoughts started changing in part back in 2013, when we were able to capture this structure of the F glycoprotein of RSV in its prefusion conformation. Historically, this virus had evaded any kind of effort at vaccine development. And the F protein had been used many times as a vaccine antigen. But it turns out that it was always used in this form [see slide #15].

We found this prefusion form of the F as it sits on the viral membrane. At the apex it has a neutralization-sensitive epitope to which antibodies are typically up to 100 times more potent than the one to the licensed monoclonal antibody, palivizumab, that binds more down here.

Finding this neutralization-sensitive epitope, we wanted to test it as a vaccine concept. Because typically, as I mentioned, even in a spontaneous way, without any cell receptor, this protein has a tendency to rearrange into the postfusion molecule. And these apical epitopes are lost when that happens.

This is the molecule used in these prior vaccine trials, at least in five different episodes – and only able to boost responses by about two- to three-fold. But learning how to stabilize this with the c-terminal trimerization domain and internal disulfides and cavity-filling mutations, and holding this and its prefusion conformation, we were able to show that this now could boost with a single injection, even without adjuvant, over 16-fold neutralizing activity, which made it a much better vaccine candidate.

Just to clarify how this happens, and why the conformation is so important, I am showing you a cartoon here created at the Rocky Mountain Labs. You have to target the protein in its original, native, prefusion conformation, shown here [ibid.].

This is because this dramatic rearrangement, in which it grabs the host cell membrane and pulls it together so that viral genome can enter, results in a protein that just has a dramatically different set of surfaces and a set of different B cell or antibody targets.

These class I fusion proteins are common to many of the envelope viruses that we care about making vaccines to – influenza, HIV, Ebola, and Lassa. But these three, in particular, we have focused on – not only RSV but some parainfluenza viruses or paramyxoviruses, and now coronavirus.
The thing that makes these similar is that there is functional homology, but there may be different domain structures like we see in coronavirus that are different than these. They have shared motifs and this functional homology. And all have these internal cleavage sites that expose the hydrophobic fusion peptide that allows these heptad repeats then to pull the cell membrane. It is pierced by the fusion peptide together to the viral membrane that is anchored in this transmembrane region.

All of these proteins work in a similar fashion. And maintaining that original prefusion conformation turns out to be important.

We have done studies with paramyxoviruses, including Nipah as a prototype, but also mumps and measles as new potential approaches for those pathogens. And paramyxoviruses have not only a fusion protein but also an attachment protein that can be given different names.

These fusion proteins work just like I just showed you with RSV. And the attachment proteins are often tetrameric or dimer-type structures and sometimes determine viral tropism.

First we showed that these prefusion F-molecules stabilized are much more immunogenic than the native wild-type F, and certainly better than the postfusion F. We designed vaccine antigens based on either the pre-F or hexameric G. In some cases a G is a better target, and in some cases the F is a better target.

We also made these chimeric molecules in which the pre-F can be connected through a fold-on trimerization domain to the attachment protein. We have learned now that this can be made either as a protein or delivered as an mRNA and effectively prevent things like Nipah virus, which we have tested now in ferrets.

**Coronavirus Origins and Phylogeny**

We also applied this to coronavirus. Because about the same time we were finding the RSV-F conformation to be so important, MERS coronavirus emerged in the Middle East. And it was the second major beta coronavirus to emerge over those 10 years since the first SARS in 2002 and 2003.

Since there was no structural information yet on the spike protein of coronavirus, we started a program there. I will tell you about that in just a minute. But we have endemic coronaviruses, either beta coronaviruses or two alpha coronaviruses, that circulate every year and that have entered the human population over the last several hundred years.

Now we have had these two new coronaviruses over a 10-year span. And we expect that this could be a problem in the future. So the program was in part to demonstrate that the stabilization of the prefusion form of the spike would be a better vaccine antigen and a different envelope virus – but in part because coronaviruses looked like they were something that could re-emerge [see slide on next page].

**Learning from the HKU1 Virus**

Failing on the MERS and the SARS structure, initially we turned to HKU1 and one of the endemic beta coronaviruses. In collaboration with [University of Texas-Austin Associate Professor] Jason McClellan, who has also been a long-term collaborator on the RSV work and other structural work, and Andrew Ward, who headed cryo-electron microscopy at Scripps, we were able to get the structure of the spike of the HKU1 virus [see slide #22].

It turned out to be a very interesting molecule, and different than other class I fusion proteins we have found. It not only does the rearrangement for membrane fusion, but it has these other very interesting dynamic properties in which the receptor binding domain [RBD] is woven around the adjacent protomer.
It has to come up in order to meet its receptor. In this case, for the SARS coronavirus, it is ACE 2. So without that RBD coming up, it cannot interact with ACE 2. And once all three of these come up, we think it opens the S1, the top part comes open and falls off of the S2, which is down here. That is the fusion machinery that then determines how the virus gets into the cell.

I do not know if you can appreciate these subtle movements, but the N terminal domain shown in blue, and some of these subdomains down here in grey, you see that they have to move. Some of these elements have to move in order for this RBD to come up.

So there are all sorts of subtle changes and mutations that can either make this come up or down more easily. Some of those, like the 614-G that makes this in the up position more often may make the virus maybe a little bit more successful on infection. Others, like the 501 mutation at the tip here might make it have higher affinity to be more successful on infection. Some of these mutations facilitate entry.

It turns out that we found that adding two prolines to the top of the central helix to prevent stacking of this heptad repeat was able to stabilize this molecule in its prefusion conformation and preserve these neutralization-sensitive epitopes at the apex.

It turned out that those same two prolines in the analogous position were able to stabilize MERS and SARS and a number of other coronaviruses. Not only did it stabilize structure, but it looked like it increased overall expression of the protein from transduced cells.

In the case of MERS, S-2P, the two proline mutation, had expressed at a 50-times-greater level than the wild-type protein. This means it could also create an advantage for gene-based delivery approaches. As I mentioned, it was able to stabilize many other viruses, so we were able to get the structure of the MERS spike and the SARS spike and other endemic coronavirus spikes.
Even an alpha coronavirus, veterinary coronaviruses, even pre-emergent bat-derived coronavirus spikes could be stabilized with this same two proline mutation. So we had a lot of confidence that that could be a generalizable approach for beta coronavirus spike antigen design.

**Ongoing Moderna Collaboration on mRNA Prototype Approach**

After our experience with Moderna during 2016 and zika, seeing how potent their mRNA delivery approach could be for vaccine antigens, we started a collaboration with them on both paramyxoviruses and coronaviruses to explore whether the prototype approach could be applied and just to demonstrate that it was feasible.

Using Nipah as the prototype for paramyxo and MERS coronavirus as the prototype for corona, we had them make mRNA delivery vectors that we tested in mice. And you see in coronavirus a 0.1 or 1-microgram dose, two doses in mice, were able to protect against infection with the MERS coronavirus in these human DPP4 transgenic mice.

They prevented: ● virus replication in the lung ● disease expression measured by hemorrhage score, and ● weight loss. And even in the dose where there is breakthrough, at the 0.01-microgram dose level, where you did even get some evidence of disease, the partial immunity led to partial protection. It did not lead to any kind of disease enhancement. So we thought the mRNA approach and its basic T cell pattern of induction was going to be a safe approach for delivery, even in a case of breakthrough infection.

**Entry of the Coronavirus Pandemic onto the World Stage**

Then as everyone knows, at the end of 2019 this new outbreak was reported, and it turned out to be a beta coronavirus. We learned that around January 6-7, 2020. We had been planning to start the Nipah virus vaccine antigen in a phase I clinical trial with the Moderna mRNA, but on January 7 we decided to flip the demonstration project back to coronaviruses. So we waited for the sequence to emerge and applied it to this new SARS-2.

There are several reasons to go fast. At the time that happened there were only a few dozen cases. So we did not really know if it was going to be a problem or not locally. But we wanted to do it as a demonstration of this pandemic-preparedness approach.

Since then, we have learned it really is a problem. I am just showing you representation of some of the deadliest plagues and pandemics in history. Many of these were caused by *Yersinia pestis*. The Black Death in the 14th century and other plague events were very large and deadly pandemics.

There have been a couple from other viruses like smallpox that have killed millions and millions of people, or HIV, which over the last 40 years has killed upwards of 25 to 35 million people.

These others are respiratory viruses, like influenza, or now coronavirus. Among those, aside from the 1918 influenza pandemic, which killed maybe 50 million people on earth, these other pandemic events, like the Asian flu in the ’50s or the Hong Kong flu in the ’60s, coronavirus has already killed more people than these other pandemic threats in modern times – over two million people on earth have now died in this coronavirus pandemic over the last year. So there is a reason to have urgency about this problem and to try to speed vaccine delivery [see slide #27].
We also see a changing pattern, where coronavirus is not only infecting in spring and summer, which is a bit unusual, but now it has even reached a steeper increase in its exponential spread through the population as it is going through these winter months. So we started this as a demonstration project, but it obviously became a much more serious development effort.

Identifying SARS-CoV-2

I want to point out some things about the coronavirus. This is an airway epithelial cell, a ciliated airway epithelial cell, that has been infected with the SARS-CoV-2 virus. This is an image that was captured by people at UNC associated with Ralph Baric.

These viruses coming out of this ciliated cell can be seen here in greater detail [see slide #29]. If you look at it more closely, these are about 80-nanometer spherical objects with these large protrusions, about maybe 22-24 spike proteins per particle.

The spike protein has become the major target for vaccine development. It is the major mechanism for entry of viruses. It is the one that is most exposed on the surface of the virus.

Global COVID-19 Vaccine Landscape

So in this amazing global response that has included well over 200 different vaccine efforts, more than 173 in pre-clinical evaluation, and now probably more than 64 in clinical evaluation, most of these have focused on the spike as the primary antigenic target.

Many of these have already achieved status in phase III or large efficacy trials, as you know: ● nucleic acid approaches ● recombinant vector approaches, and ● recombinant subunit protein approaches.
Many people have been concerned about the speed at which this has gone, and the level of confidence has been low, especially in some communities. So it has been important for us to try to explain why this has been able to go as fast as it has – partly because of the history of work that has already been done, but partly because of these new technologies. Applying all of these – either all the pre-existing public-private relationships that had existed, the prior experience with responding to pandemics, made a difference.

These new technologies to rapidly manufacture, the thinking and planning behind prototype pathogen approaches, this idea of structure-based design, rapid human monoclonal antibody discovery, and even the old work on vaccine-enhanced disease from RSV – all were in place and able to be applied almost immediately to this new virus. So there was prior work. It has not just been a one-year effort [see slide #32].

The COVID-19 Vaccine Development Timeline and Milestones

But it has gone fast, and these earlier efforts informed all of this. Because when the sequences came on the night of January 10, we were able to order the sequences on January 11, Saturday morning – to order things we needed.

We were able to order what we needed to make protein, for structures, for assays, for probes to search for new B cells and new monoclonal antibodies, to design vaccines, and even to design assays for making pseudo-viruses for neutralization. So all of that could be ordered immediately. And on January 14, Moderna started manufacturing at risk GMP clinical-grade product to start a phase I clinical trial within 65 days.

In the meantime, we were able to make the protein. Jason McClellan solved this structure with Daniel Wrapp at UT Austin, with our collaboration. We made ELISA assays and confirmed immunogenicity in animals. All of this happened before the phase I trial started. And phase III started within about 6 and a half months.
Likewise, because we had already had a collaboration with AbCellera for looking for cross-reactive coronavirus antibodies, we gave them a new probe and we gave them PBMCs. Within just a few weeks, we had a number of candidate antibodies that were picked up by Lilly and improved and who rapidly manufactured and took these into trials. And their phase III trial was able to start within about five months.

You just heard in the last few days that not only has it worked to prevent progression to hospitalization in people with moderate to mild symptomatic coronavirus, but it also looks like it is going to work effectively as a preventive prophylactic passive immunization.

We think everything starts with the protein. Knowing that it is in the right conformation gave us a lot of confidence. We were able to see the conformation, the initial conformation, from Jason around January 31. That gave us confidence to make these diagnostic assays like we did with CDC, or discover these monoclonal antibodies, or start a vaccine development program with Moderna, that at the time was a small-to-medium-sized biotech who had learned how to make stable mRNA delivery vectors.

Since then a number of other groups have gotten into advanced-phase testing. Many of them have used this stabilized version of the spike that we think makes a better vaccine antigen – including the Pfizer, BioNTech mRNA, the Janssen advector, or the Novovax and eventually Sanofi recombinant subunit proteins. All are going to have the spike stabilized in the prefusion structure that we think makes a better antigen.

Combining what we see is the rapid manufacturing and delivery approach that is also a very simple and elemental approach that is maybe the simplest approach of all to make protein, in which you just deliver mRNA as a single stranded mRNA into the cell in this lipid nanoparticle that has been made as a protein in the case of Moderna, Pfizer, and BioNTech.

It is a membrane anchor protein that sits as a stabilized trimer on the cell surface. It elicits an antibody response. And in this case, it was based on the work on this prototype pathogen preparedness, and these technologies that have been developed over these last 10-20 years.
mRNA Immunization Strategy

One of the advantages of this type of RNA that both Moderna and Pfizer are using is that it is designed with a modified nucleotide. It is a 1-methyluridine ... that is used to make the mRNA. And that helps it avoid some of these pathways that all lead to type 1 Interferon induction and effector functions.

So being careful to eliminate the double-stranded RNA or byproducts of the manufacturing and being careful to manufacture with this 1-methyl modified nucleotide, you can avoid signaling largely through the TLR7, TLR3, or these RIG-I/MDA5 pathways, and avoid a lot of the type 1 interferon that could maybe more rapidly clear the transduced cell and reduce the amount of protein expression.

There are other ways to deliver RNA – either with the unmodified nucleotides, or even in an amplitron that comes from alpha viruses that can increase or amplify the message and produce a lot of protein rapidly. This is just one way of delivering mRNA.

But in this case, we have tested for immunogenicity in mice, monkeys, and humans, and all the cases have shown that the response is either equal to or at the upper end or exceed those in convalescent sera. Even in humans, when you look at the neutralizing activity, after the second dose, these responses exceed those at the median of the convalescent human serum, even including people with severe disease.

We have been able to show protection in mice and monkeys in both the lower and the upper airway. And also in terms of safety, trying to avoid some of the pitfalls of the original whole inactivated virus RSV program in the ‘60s that led to the enhanced disease, these mRNA approaches in particular create a very TH-1-biased T cell response.

These have been surprisingly immunogenic, even in the elderly, in the 50, 60, 70 and even greater than 70- year-old age groups, compared to the responses in the young adults as shown here. And the T cell responses were equally biased towards the TH-1 responses in these subjects [see slide #37].
Durability of Antibody Response

We now have data that goes out to day 209, about 6 months after the second dose. This data showing both ELISA responses and pseudo-virus neutralization and two different types of live-virus neutralization just shows that, after the second dose peak of response, antibody responses are maintained relatively well through day 119 – giving us some encouragement that their ability of protection may be able to last at least through a season [see slide #38]. As you know, we have to wait to see what happens next year.

The phase III trials started July 27, both for Pfizer and for Moderna. And in early November, we learned from the interim analysis that it looks like even after the first dose some level of protection was achieved. Because this line of cumulative infections, symptomatic coronavirus infections, the placebo line is separating from the vaccinee or mRNA line. The second dose came in around day 29.

As you all know as well as I do, this was highly effective, in the 94-95% range. All 30 cases of severe disease, which meant oxygen levels below 93% saturation or hospitalization, were in the placebo recipients.

The VRPAC met on December 17 for the Moderna product – a week earlier for that on the Pfizer product. Then FDA authorized it for emergency use the next day on December 18. And of course, Dr. Fauci, who everybody follows, was immunized just a few days later.

Now, many of my staff members and friends and colleagues have been immunized.... These are some of our nurses. This young student is one of the ones who made the initial batch of protein – Olubukola Abiona. Kizzmekia Corbett is a fellow in my lab who has led a lot of this work from the early days, and even before this outbreak started. And John Mascola is our VRC director [see slide #41].

Conclusions and Thank Yous

I want to emphasize that this rapid response was based largely on prior fundamental basic and translational research that gave us tools for both precision and speed – also because these public-private partnerships had been already established for at least three years before this event happened. We ended up with a good result, even better than we had hoped.

So with these new technologies, I want to emphasize that I think prototype pathogen preparedness is feasible, even for the other viral families that remain out there.

I want to thank: ● the people and program heads I work with everyday ● Jason McClellan has been an important collaborator on all of the structural work ● the graphic artists at Rocky Mountain labs ● my lab, especially Dr. Corbett, who is hiding here, who helped in this coronavirus program over these last five or six years ● of course Moderna ● our close academic collaborators, not only at UT Austin with Jason, but at Vanderbilt with Mark Dennison and at UNC [University of North Carolina] with Ralph Baric, and ● all of these groups, especially the extramural division of microbiology and immunology and NIAID who took on the IND for the phase I trial and helped get that done through their network of clinical sites. [See slide #43 for a more complete listing of VCR staff involved.]
Barriers to Clinical Trial Acceleration

Q: What have been the main barriers to going faster in the clinical trials? For example, was it product development, manufacturing and scale-up, or regulatory?

I have to say that the regulatory people have been working closely with scientists all the way through this process. It has been quite a remarkable thing. I would say the greatest barriers have been our own conventional thinking about how this should happen.

Even in the beginning, at the phase I trial, I think we could have started two weeks earlier. But people just were not used to moving quite that fast. And at that time, the outbreak had not really spread much globally. So I think the thing that prevents us from going faster is mostly our own way of thinking about how it should be done. I really think a lot of this could always go faster.

With the RSV program, for instance – where we think it is also going to be effective – it took us three years to get into a phase I trial. We are just now into a phase III. And we will not have those results for a couple more years. So that is a more typical approach.

The thing that made this feasible to compress all the animal studies and clinical timelines was the influx of cash. The ability for the companies to make decisions that were all happening in parallel and not sequentially is what allowed them to go fast. I think that is usually the major barrier typically to going fast – you do not want to put the money at risk, so you do things serially. In this case, a lot of time and effort and money was put at risk. But I do not think that any of the safety steps have been skipped here.

Q: Do you think what we learned with conventional thinking and parallel pathing is here to stay? Will that be with us for the future to meet the next big challenge that comes our way? Do you think we have gone that far in this?

I hope that it has at least changed some of the paradigms and ways of thinking about what is possible. I do not think we will always be faced with this kind of a crisis. And I do not think there will always be billions of dollars provided ahead of time at risk, not knowing whether any of these things would work. So I do not know that it will be conventional to go this fast, but at least we know that it is possible now to go this fast. And there is a little bit of a template for how to do it. But I think that under normal circumstances it is unlikely to go this fast in the near future.

mRNA Technology As Go-To Vaccine Approach

Q: Is mRNA technology going to become the go-to approach for viral vaccine development?

I have always thought that nucleic acids were the most elegant way to deliver a vaccine. We worked with DNA vaccines for 30 years, and it has only really been figured out how to stabilize mRNA and deliver it effectively in the last five or ten years.

But nucleic acid delivery approaches are, in my way of thinking, the most elemental way of getting a protein made as a vaccine. It creates a platform technology that does not require a lot of modifications. And it allows the cells to make it themselves. It creates not only the protein for an antibody response, but it induces everything we need to make T-cell responses – both CD4 and CD8 T-cell responses. So I think it is a very effective way of delivering a protein.
In some cases, it may be the right way to deliver a vaccine antigen. In this case, I think it was. I think for some of the flaviviruses, like Zika, if you can produce subviral particles, that it may be a good approach for that. I do not yet know whether it is the best way to boost. If you have pre-existing immune responses to things, like we do to RSV and flu, I do not know if it is better to boost yet with a nucleic acid or a protein. Proteins are a very good way to boost responses.

I think all of these different technologies have their place. I think we have to figure out how they are fit for the purpose they are intended for. But mRNA clearly is feasible. Now we know how to scale it up. And so I think it is going to be one of the important tools going forward.

**Addressing Vaccine Use Hesitancy**

**Q:** When is NIAID going to address vaccine hesitancy in the general population?

Well, I think a number of us are very devoted to that. I think Dr. Kizzmekia Corbett and I are on webinars, if we add them up, almost every night of the week, trying to help inform people about what this process is like and how it works. And Dr. Fauci [NIAID Director], Dr. Collins [NIH Director], many people at NIH, Dr. Mascola, my director [at the Vaccine Research Center], are all very invested in community education.

Maybe we have an opportunity during this crisis that all of us are experiencing together to make changes in the way people think about vaccines in general and the way they might trust. We may be able to gain a little bit of trust back in the federal government and the biomedical research enterprise, and hopefully we can turn that needle back a little bit more toward the trust. So there is a lot of effort being put into this.

The network groups also have a large community education effort – not only for bringing people into the trials, but to help them understand about how the vaccines were made and how they can be trusted. So the goal is to help people be better informed so they can make their own decisions. Some people may still decide not to get a vaccine.

Everybody is going to be immune in a few years, and you are either going to get that way by infection or by vaccination. And the infection gives you a one or two percent chance of dying. The immunization is giving you a couple of chances out of a million to have an allergic reaction. So I think people have to decide which one is the safest.

**Why no HIV Vaccine**

**Q:** Do we understand why we do not have an HIV vaccine?

I can tell you a lot of reasons why we do not have an HIV vaccine. They all involve biology. That virus has so many ways of immune evasion. Even just based on the antibody responses, it can do the conformational evasion that RSV does. It can do the antigenic variability and immune dominance of misdirection that influenza does. And it can have this extensive glycan shield and hide all of its important epitopes, in some way like coronavirus does, which is also heavily glycosylated.

So HIV has all of those effects on antibody response targeting its envelope. And so far we have not been able to solve all those different biological problems with the same product. In addition, it is a virus that people cannot really clear with their own natural immunity. As Dr. Fauci has said many times, that is not a good sign for a vaccine development. If you cannot clear a virus with natural immunity, it means a vaccine immunity may be hard to achieve.

In this case, we also need very effective T cells that can be easily escaped by this HIV. It has figured out ways to infect our main cell for immune induction, the CD4 T cell. And it has figured out a way to evade most of our important adaptive responses, like the antibodies and CD8 T cells. So it is just a fundamentally different biological problem. Hopefully, as we learn more about each of these other, simpler viruses, we can take all that and apply it back together against HIV, and eventually have a solution. But it is really not easy.
Vaccine Strategy for COVID Variants

Q: What type of vaccine strategy is more efficient against the new variants? For example, mRNA, adenovirus based sub-unit, or the inactivated virus?

These new variants are coming up. It is not that unexpected. It is an RNA virus. It is a large RNA virus. Even though it has an editing function in its polymerase, it still makes a lot of mistakes during replication. So the more it grows, the more it spreads, the more chances it is going to have to adapt and change and evade both our innate and our adaptive immune responses. Not to mention that it can learn how to attach or infect better. So we need to try to keep it from replicating so much so that we do not have so many things to solve.

We do have approaches now that we think can work. It depends on how quickly you change course. But the mRNA is faster to make. The vector-based approaches are probably second-fastest to make. Then making stable cell lines or making new vectors are probably the third fastest to make, just like you see the rollout happening. This is all based on how easy it is to synthesize and manufacture.

So depending on how you start and how you decide when you have to change vaccines, if you do have to, to adapt to these different variants, I think that is the order of how fast it can go. It is obviously something we could easily switch to. It is just that it would make a delay in the final manufacturing.

And it creates a real dilemma for the regulators, I think, because if you put a new spike protein in with nine amino acid changes, and it is 2-1208 amino acid ectodomain, is that enough change to require a whole new set of regulatory decisions? Or is that something you can say, ‘In this setting, we have to just switch sequences and keep going.’ That is going to put a lot of strain on the regulatory apparatus, and I appreciate that. But it will be interesting for me to know and hear what your plans are for that kind of decision-making.

Increasing Mutation Coverage

Q: Can different sequences from different variants be combined in one vaccine to reduce risk of escaped mutations?

That could be done. I think one of the questions that faces us as vaccine developers is when you would make the decision to change the antigen. Because you want the new antigen to also be able to protect against the old viruses. Because not everyone is getting infected with the new strains. There is not very much of the South African or the Brazilian variant yet in the US. So you do not want to make that strain and then have it not address the former viruses. So some of those studies are being done now.

You have probably seen a lot of things have been posted on the bioarchives over the last few days, showing whether vaccine sera can still neutralize the viruses or pseudo viruses with these new sequences in them.

Some sequences are more dangerous than others – like in my opinion the 501 sequence is more about better affinity between the RBB and the receptor. So it may be for better ability to attach or infect. Some sequences may truly be immune-escape. The 484 DDK variant is the thing I think we are most concerned about in that regard, because some of the more potent neutralizing antibodies recognize around that one amino acid.

I think as long as we have vaccines that have a lot of antigenic content that are inducing antibodies to a lot of surfaces and parts of the different spike proteins, that we have a chance of having immune responses that can resist evasion or escape. So the question is just when is there too much change that forces you to change vaccines. I do not think we are there yet, but we may get there over the course of the next few years.