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Paul Offit, MD
Director, The Vaccine Education Center
Children's Hospital of Philadelphia

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Webinar

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President & Chief Executive Officer
Memorial Sloan Kettering Cancer Center
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Introduction

President Barbara Van Allen

Good afternoon and welcome to the 597th meeting of The Economic Club of New York in our 114th year. I'm Barbara Van Allen, President of the Club. As many of you know, The Economic Club of New York is the nation's leading nonpartisan platform for discussions on economic, social and political issues, and our mission today is as important today as ever.

A special welcome to members of the ECNY 2021 Class of Fellows – a select group of very diverse next-gen business leaders, and welcome also to graduate students who have joined us from CUNY Graduate Center and Rutgers University.

I'd like to now introduce our special guest, Paul Offit. Paul is the Director of The Vaccine Education Center at Children's Hospital of Philadelphia as well as the Maurice R. Hilleman Professor of Vaccinology and a Professor of Pediatrics at the Perelman School of Medicine at the University of Pennsylvania. He is a recipient of many awards, including the J. Edmund Bradley Prize for Excellence in Pediatrics from the University of Maryland Medical School, the Young Investigator Award in Vaccine Development from the Infectious Disease Society of America, and a Research Career Development Award from the National Institutes of Health. Paul has published more than 160 papers in

medical and scientific journals in the areas of rotavirus-specific immune responses and vaccine safety.

The format today will be a conversation, in which we're fortunate to have the President and CEO of Memorial Sloan Kettering Cancer Center and Club Trustee, Dr. Craig Thompson, as our moderator. We're going to end promptly at 2:45, and as a reminder, this conversation is on the record and we do have media on the line. Without further ado, Craig, I turn the mike over to you.

Conversation with Dr. Paul Offit

CRAIG THOMPSON: Thank you, Barbara. And I just, before I turn it over to Paul with the first question, I just want to add to the accolades that Barbara provided for Paul's career. Beyond the positions that he holds and his scholarship, he's also produced nine books that explain the benefits of vaccines as well as address the public's scientific and non-scientific concerns around vaccine efficacy and side effects. He has practiced what he preached. He's a former member of the Center for Disease Control's Advisory Committee on Immunization Practices, and he's a current member of the FDA Advisory Panel on Vaccines, which provided their expertise at each of the vaccines that we've seen be approved over the last several months of coronavirus.

Beyond that, Paul has real-world experience himself in all aspects of vaccine research and development. He was one of the developers of a safe and effective vaccine for rotavirus. Rotavirus is now given to newborns in over 80 countries as a result of Paul's work because rotavirus infections are the leading cause of death and childhood diarrhea and was responsible at the time of his vaccine development for over 600,000 deaths annually worldwide. The development and implementation of his vaccines starting in 2006 have saved hundreds of lives daily in the developing world. The vaccine, RotaTeq, was a triumph of academic, public and private collaboration and provides us a blueprint for how vaccine development and deployment on a global scale can actually be achieved.

So Paul has graciously agreed to join us today and share his expertise on the role of vaccines in controlling the current Covid-19 pandemic. Paul, welcome to The Economic Club of New York.

PAUL OFFIT, MD: Thank you.

CRAIG THOMPSON: Despite the rollout of multiple vaccines in the last year that you were part of the approval process and the fact that 31 million Americans have had Covid-19 and 133 million have received a vaccine to date, the U.S. seems to be experiencing another wave. I don't know whether it's an exit wave, as people were

excited to see spring, and come back, or it's post-holidays. But can you just give us some idea of when we're going to get, or are we going to get to this herd immunity we've heard so much about from epidemiologists over the last year?

PAUL OFFIT, MD: Right, so I think right now there are three things that are working against this virus. The first is the weather. I mean if you look at what happened when this virus came into the United States in the first week of March of last year and started killing people, we went from 1,000 deaths a day to 2,000 to 2,500 deaths a day as we moved into March and April. And then the numbers started to come down.

So for the summer months, June, July, August, we rarely ever had more than 1,000 deaths a day and usually it was hundreds of deaths a day, even though we had a fully susceptible population and even though we didn't have vaccines. That's because this is, at its heart, a winter respiratory virus. It doesn't do as well in the summer months. It still can spread in the summer, which is true of other winter viruses like flu, just much less so. So I think that's what happened.

Then came November and you just saw; we went from 1,000 deaths to 2,000 deaths to 3,000 deaths to 4,000 deaths to 4,500 deaths. And then as the weather started to get a little warmer, it started to come back down again. So now we're at sort of hundreds of deaths a day. That's one. I think weather matters.

Two is I think what you had mentioned correctly, that 30, roughly 31, 32 million people have been infected with this virus, but that's just people who have been tested and found to be infected. When they do antibody surveillance studies, which is a more accurate way of saying how many people have really been exposed to this virus, that number is probably off by a factor of three. There's probably between 90 and 100 million people who have already been infected with this virus which is like another 30% of the population.

And the third thing working against this virus now, as you said, is the vaccine. I mean you have at least 25% of the population that's fully immune and there's overlap obviously between those naturally infected and those immunized because some people who were naturally infected have gotten the vaccine also. So I think we're probably at about 40% population immunity from vaccination or natural infection.

By the summer, we will have enough vaccine for everybody and what we need to get to, I think, is at least 80% population immunity to significantly slow the spread of this virus. And the way you're going to know whether or not we're successful is when November hits. Because if we're successful to get to 80%, when winter comes we will see a bump in cases. But if we're not successful, if a critical percentage of the population chooses not to be vaccinated, or we're surprised that immunity is short-lived, then you'll see a surge next winter. I think the predications about this so-called Category 5 hurricane this

spring is wrong. I don't think that's going to happen. What worries me is that we'll be sort of lulled into this notion that it's not that big of a deal if the numbers sort of stay low through the summer, but we need to get vaccinated. We need to get 80% of this population immune by either vaccination or natural infection.

CRAIG THOMPSON: Well, Paul, you work at a children's hospital, the Children's Hospital of Philadelphia, which has been a leading vaccine expertise center, and you run The Vaccine Education Program. More than 20% of this country are under the age of 18. When are they going to be eligible for vaccines? What's the plan for their immunization? Kids don't get as sick, but can they still spread it? What's the position on all that right now?

PAUL OFFIT, MD: Right, so we need a vaccine for children. I mean at least 2 million children have already been infected with this virus. About 200 children have died from this virus, which compares similarly to flu, which will kill 75 to 150 children a year or chicken pox before the vaccine, which would kill about 75 to 100 a year too, and measles, which would kill about 500 a year before the measles vaccine. So just on deaths alone, I think we would benefit from a vaccine for children.

Pfizer has already done essentially a Phase 3 trial in children down to 12 years of age, in the 12- to 15-year-olds, and that trial certainly looked good. They've submitted for

approval to the FDA through Emergency Use Authorization. That should happen soon. My understanding is Moderna is weeks behind, so that should also happen soon. So I would imagine that we would have, by the summer, vaccine available for children down to 12 years of age. There are studies currently being done actually down to six months of age.

But I think that we'll have probably have data at least down to six years of age by early next year for children because I think children would benefit from this vaccine for so many reasons – getting back to school – and children can suffer this unusual disease called MIS-C, which is this multi-system inflammatory disease, which is frightening as children basically make an immune response against their own blood vessels. It's hard to watch children suffer from that disease and we've certainly had many cases in our hospital with them.

CRAIG THOMPSON: So just in terms of that, if the vaccine is going to be made available, or at least be approved for emergency use over the course of the summer, how are we going to get the word out? How are the children's hospitals thinking about getting that word out to the parents and getting immunizations going with the kids? Is there a plan for that?

PAUL OFFIT, MD: Right, so we're working on that now. See, normally when children

get vaccinated, they get vaccinated in the pediatrician's office because it becomes part of the routine schedule. That's not going to be true with this vaccine. And the reason it's not going to become part of the routine schedule where you just plug it in to vaccines that children would get, say at 4 to 6 years of age or 11 to 13 years of age, is that they're not doing concomitant use studies.

In other words, they're not doing studies looking at what happens when you give this vaccine at the same time you're giving other vaccines to make sure that you don't interfere with the safety or immunogenicity profile of existing vaccines and vice versa. So it's going to be a stand-alone vaccine. I think maybe in a couple of years, you would see concomitant use studies with the flu vaccine but that, I think, is far off. And as far as I know, that hasn't started. So I think it's going to be a challenge as to how we administer this vaccine.

And the other reason I think it can't be in the pediatrician's office is a vaccine like Pfizer is a vaccine which has to be shipped and stored on dry ice and that has a refrigerator life of five days and is a multi-dose vial. You know these vaccines are either five or ten-dose, multi-dose vials. I don't think that's possible for a pediatrician's office. So we have to find where the medical home for these children is going to be and it may be the pharmacy.

CRAIG THOMPSON: So what's your advice to parents who are looking forward to sending their kids back to school for all the important reasons we need to get kids back in school and the economy going about how that's going to be accessed and what they should be prepared for in August and September? What are they looking at?

PAUL OFFIT, MD: I do think that we're going to do well over the next, say four or five months or so. I think people will feel better about this. And we're not helpless, I mean you can still wear a mask. You can still physically distance as a way to avoid this infection because I think that when September comes – not all children – certainly down to six years of age are going to be vaccinated at all. But I don't think that means that we can't go back to school. I think we can go back to school. We just have to do it, you know, carefully and thoughtfully.

CRAIG THOMPSON: And you've thought a lot about this. We have close to 25%, if you believe the numbers that are circulating in the press right now, that are vaccine-hesitant at all ages. What do you say to them about the importance of vaccination as we move forward?

PAUL OFFIT, MD: This actually scares me more than the variants. I mean there are two things that stand in the way of getting adequate population immunity. One is the variants, that this virus continues to mutate to the point that it is no longer neutralized by

antibodies induced by natural infection or immunization. The second thing is this, what we euphemistically call, you know, vaccine hesitancy, which I prefer to call vaccine denialism because that's a little closer to what it is. I mean I think you can divide people into two groups, those who are hesitant.

One is the vaccine skeptic – fair enough. You should be skeptical of anything you put into your body, including vaccines. If you had asked me last September, would I get a Covid-19 vaccine, my answer would be let me see the data. I don't know, let me see the data. But now you have data on the two mRNA vaccines. You have a lot of data. You know that it's 95% effective. You know it's 95% effective against all manner of illness – mild, moderate or severe disease. You know it is to some extent effective against asymptomatic infection where you shed infectious virus. You know that it's effective in people over 65, as effective in people over 65. You know it's as effective in people who have a variety of comorbidities which put them at risk, like obesity or chronic lung disease or chronic heart disease.

And you know that it was safe in tens of thousands of people before it was approved. Now you know it's safe in tens of millions of people. I think there have been more than 200 million doses of this vaccine have been out there. This vaccine is safe. It's ridiculously effective. I don't know what people want. On the Vaccine Advisory Committee, we were told that we would accept a vaccine that was at least 50%

effective. Last summer, Dr. Fauci predicted or hoped, he said he hoped that this vaccine could be 70% effective. It's 95% effective. It's been in more than 100 million people and it's safe. At this point, if you're a skeptic, that skepticism should melt away.

So now let's talk about the second group, what I would call the vaccine cynic. These are conspiracy theorists. They're denialists. They just don't believe the data. I saw an interview on television where someone said I don't believe the data. So how do you convince that person? You don't. I mean as Neil deGrasse Tyson says, if people reach a conclusion without using reason or logic, reason or logic is not going to talk them out of it. So now you're at Plan B. And I think Plan B is you compel them to do it and I think that's where the mandates will come in, and I think that's going to come from the private sector. That's not going to come from the public sector. You're already seeing it. You're seeing it at universities, for example, that say you can come back to school but get vaccinated. Otherwise, it's still distance learning for you.

CRAIG THOMPSON: So if we address the first group and some of their concerns, which are just the people that are truly hesitant, are waiting for that data, one of the concerns they have is that this was, the vaccine was rapidly developed in less than a year and we don't know the long-term side effects. I hear it particularly from young people thinking about starting a family or having a family who want to know. This is a vaccine, the ones you just talked about, contain nucleic acid, and they worry about

whether they're going to pass it on to their kids or it's going to damage their own DNA and affect their ability and damage their genes and affect their longevity. So how do you answer those kinds of people who just want more information about that particular issue? This is a new form of vaccine as we've been told, the mRNA vaccines.

PAUL OFFIT, MD: Right. So, it's understandable. I mean, you know, I've worked on a vaccine, as you mentioned, at Children's Hospital of Philadelphia. I was fortunate enough to be part of a team that created the strains that became the rotavirus vaccine, Rota-Teq. That was a 26-year effort. That's about average for what you expect for a vaccine. Here you had a vaccine that was, where you had that virus in hand and sequenced in January of 2020. There were two large clinical trials that were completed 11 months later. This has never happened before. And so people could reasonably worry. Right? The phrasing around it was also scary. Right? Operation Warp Speed, the race for a vaccine, who is going to be the first to cross the finish line?

So here's what I would say. I was on the committee, I'm on the FDA Vaccine Advisory Committee. We looked at these data. Here's what's not different about this process, this EUA process, as compared to any typical licensed vaccine. One is the size of the trials. The 30,000-person trial of Moderna, the 44,000-person trial of Pfizer, the 44,000-person trial of Janssen, Johnson & Johnson is the size of any typical pediatric or adult vaccine trial. The safety follow up was the same – two months after the last dose. If you look at

all the serious side effects that have been associated with vaccines, and there are serious side effects occasionally with vaccines, they all occur within six weeks of the dose. So you may not pick up a rare adverse event in these tens of thousands of person trial, but if they occur, they'll occur within six weeks.

And so the only real difference is length of time for efficacy. When we approve those vaccines through EUA, we could say they were effective for a few months. We didn't know whether they were effective for a year or two years of three years. On the other hand, you're not going to do a two or three-year study for a virus that had already killed about 500,000 people. You're going to say, look, you have this high level of efficacy and you have this so-called cellular immunity which predicts generally longer-lived immunity, and we're finding that. Already, you know, the first effectiveness study that just came out at the end of March shows that it remains highly effective in a real-world situation.

In terms of your question about DNA, this is the question I get asked the most, right? Because normally if you're making a vaccine, you're trying to induce the immune response against the surface protein of the virus. That's typical. So in this case, the SARS-CoV-2 surface protein is called the spike protein. Normally what you do is you give that spike protein either as a purified protein, which is the way we give the hepatitis B vaccine, or you give it as a live weakened form of the virus, which is the way we do the measles vaccine, or you give it as a whole killed form of the virus, which is the way

we give the inactivated polio vaccine. But that's not what we're doing here.

What we're doing with these mRNA vaccines is you're actually given a small piece of genetic material that then enters cells and then you make, your body makes the SARS-CoV-2 spike protein. Then your body makes antibodies to that protein. Now the technology, messenger-RNA, is not new. I mean it's been around for more than 15 years. It, however, has never been used to make a vaccine before. There's no commercial experience with an m-RNA vaccine. But there's plenty of experience with m-RNA. I mean you have 200,000 copies of messenger RNA in every one of your cells, and the messenger RNA in your cells is translated to proteins and enzymes that help your cells survive. So now you're just giving that messenger RNA, which lives in the cytoplasm of the cell, probably has about a 48-hour life in the cell before it breaks down. So it'll make protein, SARS-CoV-2 spike protein for about two days and then it'll break down, which is true for all the other m-RNAs.

In order for it change your DNA, because remember this is RNA, it's not DNA, it has to get into the nucleus, which means it has to cross the nuclear membrane, which means it has to have a nuclear access signal, which it doesn't have. So it can't get in. Even if it got in, which it can't, it has to be, it's RNA, so it has to be reverse transcribed to DNA, which requires an enzyme called reverse transcriptase, which it also doesn't have. Even if it was reverse transcribed, which it can't be, it still has to be integrated into DNA,

which requires an enzyme called integrase, which it also doesn't have.

So it's not like the chances of this altering your DNA are small. The chances of this altering your DNA is zero. You have a better chance of developing X-ray vision or become Spiderman if you get this vaccine than having it alter your DNA. Although just to keep, make sure we stick to the science, you become Spiderman when you're bitten by a radioactive spider.

CRAIG THOMPSON: Paul, I think that's a great answer for the vaccine-hesitant, and some of the things that I've heard particularly from younger members who are thinking about whether or not they should wait and see the vaccine. But the denialists counter your arguments by simply saying, well, if this were all you say it was, why is it not fully approved? It's only approved for emergency use. What does that mean, an emergency use approval? And why hasn't it changed if all the evidence is there that you've just summarized so beautifully?

PAUL OFFIT, MD: No, I think it's a legitimate concern. I mean people, anybody who has been paying attention to the past year knows that hydroxychloroquine was also approved through emergency use authorization, a drug that doesn't work to prevent Covid-19, that doesn't work to treat Covid-19. Yet it was approved through emergency use and then it wasn't approved and then they took it down, took it off the market. That

was an unfortunate series of events.

What I would say is this. The FDA has said now that if you can show efficacy or effectiveness for at least six months after this vaccine is starting to be used, then you can get a license. So my sense is that you are going to see these companies submit for a license over the summer and probably get a license by the end of the summer. And that will make it, I think, a lot easier for, I think it'll make it easier for the mandates. Although you can still, my understanding from two lawyers that I've talked to, one at Penn, one at U. Cal Hastings, is that the EUA doesn't prohibit you from mandating a vaccine. You can still do that. But I think it'll just make people feel better if these were licensed products which should happen by the end of the summer.

CRAIG THOMPSON: So that's really my follow-up question. What changes when the vaccines are fully approved and receive an FDA approval label?

PAUL OFFIT, MD: Now it's licensed, so now it goes through the normal biological license process, which frankly is no different than what we just did. I mean I'm on the committee, we have licensed vaccines in the couple of years that I've been on this committee. And the process by which we licensed them is really no different than this, which is to say the company submits their data, usually about 100 or 120 pages of data. And then the FDA reviews all their clinical data and then has their own 100 to 120

pages. Then about a week before we meet, we get those two data, as the public does. I mean this is put onto the FDA's website. Anybody can look at the data we're looking at. And then we sit down for a day and we go through all those data and we ask our questions to the company and we ask our questions to the FDA. And then at the end we vote.

This is the way we do it for any licensed product and it's the way we're doing it for here. The only difference here is the length of follow-up for efficacy. That's the only difference between, in this case an EUA and a licensed product. I wish there was a different phrase to use rather than EUA. Because the EUA really implies, according to the FDA language, really just implies permission to use an investigational new drug. That's really what an EUA is. And this is much, much more than that. We know much, much more than that. So I think it's unfortunate, the language. I wish we had a different phrase for this.

CRAIG THOMPSON: So let me just make sure I'm clear on this. The EUA is really because there wasn't enough evaluation of the efficacy of the vaccine against the virus, not because of the safety? You all were satisfied on the safety profile and remain satisfied on the safety profile? Is that what you said? I just want to be clear on this.

PAUL OFFIT, MD: Yes, I think in terms of safety, when you do these trials – and it's true

for every vaccine – you get tens of thousands of people. I mean the rotavirus vaccine trial was a 70,000-person trial. The human papillomavirus vaccine trial, that cancer-causing virus, was a 30,000-person trial. The size of these trials were the same But that's all you can say. You can say when you see those trials that the vaccine does have relatively uncommon serious side effect. But you really only find out about rare serious side effects after vaccines have been in millions and sometimes tens of millions of people, which obviously is prohibitive as a Phase 3 trial.

CRAIG THOMPSON: But as you said, right now over 100 million Americans have received a dose of this vaccine and we are hearing about side effects, but the mRNA vaccines have been remarkable clean. Will there be any real concern if it comes back up for permanent approval?

PAUL OFFIT, MD: Not as I see it. No. But again, I mean, we need to see all the data. So we're actually specifically told on the committee not to make any predictions about...

CRAIG THOMPSON: Fair enough, so I don't want to ask you because we want you to be part of the regulatory process. So let's move ahead. Let's say you're right, your prognostication is right that in August, one or more of the mRNA vaccines is approved. Should employers mandate vaccinations? How should we think about that? We want to get the country back up and going. What are the pros and cons about mandating a

vaccination? What's your position on that as public health expert?

PAUL OFFIT, MD: In a better world, people would look at the data. They would be convinced by the data. They would know that this is a virus that's common and know that it's a virus that can kill people or cause permanent harm and get the vaccine. In a better world, that's what would happen. That's not the world we live in. The world we live in, there's a lot of scientific denialists. People simply declare their own truths no matter how incorrect. And then because of that, there's a significant percentage of the population that isn't vaccinated, that then allows this virus to continue to spread. And the worst thing about allowing it to continue to spread is it will continue to make variants. That's why you have to stop the spread. That's why, you know, when people say, you know, what do you care what I do, you're vaccinated. Well, if you're not, first of all, there's a couple incorrect assumptions there.

One is that all vaccines are, that any vaccine is 100% effective, which is true of no vaccine. Secondly, it assumes that everyone can be vaccinated, which also isn't true. But if you're allowing the virus to continue to spread and variants continue to be generated, that's a problem. So I think we need to make a decision. But I don't think it's going to happen at the government level, the state or federal level. I think that's all going to happen at the private level and it's already happening.

I mean I work in a private hospital. We are seriously considering mandating the vaccine, which we do otherwise. We have a flu vaccine mandate at Children's Hospital. If you want to work in our hospital in any capacity – nurse, doctor, environmental services, dietary – if you walk in the room of a child, a child in our hospital who is vulnerable, you have to get a flu vaccine. If you don't want to get a flu vaccine, at our hospital you have two weeks of unpaid leave to think about it. If you still don't want to get a flu vaccine, you're fired. That's your responsibility working in a hospital because you've chosen to work around a vulnerable population of hospitalized children.

I feel the same way about society. I mean there are a lot of people in this country, probably about 500,000, who can't be vaccinated because of their chronic disease, because of their chemotherapy, whatever, because they're too young. I mean, you know, there's a lot of reasons why people don't or can't get vaccinated. Do you have a responsibility to them? Do you have a responsibility for the person you come in contact with? Is it your right to catch and transmit a potentially fatal infection? No. And I would like to think we will stand up for that, as states have.

I mean it used to be there were only two states that had only medical exemptions – Mississippi and West Virginia. I mean the answer to the question, what state has the highest rate of vaccines in the United States? Mississippi. Not one you would necessarily pick. I mean not a state that's known for its public health achievements. But

they only have medical exemptions to vaccinations. Now there's three more states that have joined that because people got tired of these measles epidemics. New York being one of them. You know that five children were in the intensive care unit a couple of years ago at NYU Langone with measles, is just pathetic.

I mean there's so much we don't know in medicine. There's so much we can't do in medicine. This we know. The germ theory is not just a theory. Specific germs can cause specific diseases and we can prevent those diseases with a vaccine, and it is not a parent's right to put their child in harm's way unnecessarily. It's not. That's what the 14th Amendment is all about I think.

CRAIG THOMPSON: So I think those arguments are winning over a lot of people. I know here in New York a number of people were waiting, but actually don't like needles, and so were waiting for a one-shot vaccine, which the great hope when it was approved, the J&J vaccine offered that opportunity. We knew over 10% of the people that were in our patient population were excited to now get in line for the vaccine and then we got these new safety concerns about the single shot vaccines. Tell me what you know about those and what should we be thinking about the side effects because we've heard that there's a set of these clotting side effects for both the AstraZeneca and the J&J single shot vaccines that were touted as making this a much simpler process. Go in and get a shot and get a result immediately over the next week of protection.

PAUL OFFIT, MD: Right. So the J&J and AstraZeneca vaccine – we obviously don't have the AstraZeneca vaccine in this country – they're both the same class of vaccine, which is to say replication-defective adenovirus vectors that deliver that gene into the cell in a different manner than the mRNA but with the same outcome, which is that your body makes the SARS-CoV-2 spike protein.

What happened with the AstraZeneca vaccine, and this was seen earlier because that vaccine was out in much larger numbers not only in the United Kingdom but in Europe, is that this vaccine can rarely cause clotting. And it's an unusual kind of clotting because it's a clotting that's associated with a decreased platelet count. Platelets are that cellular element that causes your blood to clot. So here were people that had a clotting problem but had decreased platelets so it's, thrombotic thrombocytopenia is the term. And the term that's used for this whole problem is called vaccine-induced thrombotic thrombocytopenia, VITT.

In terms of the serious clots, like a clot that can occur in your brain, what was found in the U.K. and in Europe was it occurred at about one per 250,000 people. Here in the U.S., a similar problem was found with the Johnson & Johnson vaccine at roughly one per million people. I think if, there are advantages to the Johnson & Johnson vaccine and I'll get to how we're going to handle this in a second because tomorrow is a big day.

The Johnson & Johnson vaccine is a single dose and it induces cellular immunity after one dose which a single dose of mRNA vaccine does not do. So you can have one dose of this vaccine and induce what I would hope would be at least a couple, three years of immunity. And it induces excellent levels of immunity in people who are older, which, you know, is good for people like me who are older. So the other thing is it's refrigerator-stable. That is not a small thing.

I mean the Pfizer vaccine has to be shipped and stored on dry ice. It has a five-day life in the refrigerator. The Moderna vaccine has to be shipped and stored frozen. It has a 30-day life in the refrigerator. This vaccine has a three-month life in the refrigerator. It can be shipped and stored at refrigerator temperature. There are a number of groups of people and places like rural communities, people who are sort of stay-at-home people, people who are less likely to get that second shot for whom this was of benefit.

And I think if the J&J vaccine had been the first vaccine available in the United States, we would have been having a very different discussion. The discussion would have been this is a rare, but likely real side effect of this vaccine. Here's how you treat it. Don't treat it with heparin. Treat it with either a thrombin inhibitor or with intravenous immunoglobulin. We know that now so we're not going to make people worse by giving them heparin. It's extremely rare, it's one per million. If you take a theoretical million people who are infected with Covid, 5,000 will die. Therefore, the benefits clearly

outweigh the risks, the small, but real, but excruciatingly small risk. That would have been the discussion.

But it wasn't the first vaccine. It was the third vaccine and the other two vaccines – the mRNA vaccines – don't do this. So now what do you do? And I think what the FDA and CDC initially did was they said, pause. And I'm still not sure what pause means exactly but that's what they said, pause. And then the ACIP, the Advisory Committee for Immunization Practices to the CDC last Wednesday was going to then give us a path forward which they didn't do. They just continued the pause while they wanted to gather more data, although I'm not sure what more you're going to learn. This is still going to be a very rare phenomenon. So I wish they'd given us directions. I think they will be giving us direction tomorrow, and I think that direction will be either use this vaccine but explain to people what the risks are. I mean give them, trust the American people to understand the concept of relative risk.

The second possibility, and I don't think this is going to happen but we'll see, is they may make an age-specific recommendation because for the most part, at least so far, this problem of blood clotting in a vein in the brain is generally people less than 50 and often much younger, and often there seems to be a predominance of women. So they'll say, let's say just give it to people over 50, which is what some European countries have done. The European Medicines Agency has basically left it up to countries in

Europe to decide what they want to do, some of which just give it any way, others have an age restriction or gender restriction. We'll see how this plays out.

I do think the challenge is communicating risk. It's not easy to communicate risk. It isn't. And I think when people hear the term, you know, one in a million, what they hear in that is it can happen to me. Whether it's one in a million, one in a billion, one in a quadrillion, what they hear is it can happen to me. When New York State sold lottery tickets a few years ago for a 14 million to one chance of winning, they sold it with the phrase, it can happen to you. And so I think that's how people hear these things. So I think it's a challenge to get people to understand risk. I mean you have a greater risk of being in a car accident on the way to getting the vaccine.

CRAIG THOMPSON: Well, Paul, you've been an advocate of global vaccination development to solve world health problems. This is clearly a pandemic affecting the entire world. We're going to need vaccine strategies that work throughout the world. If they put an age restriction on these kinds of vaccines, it's going to be difficult to use them throughout the world to employ it. So how are we going to think about getting vaccines out to the rest of the world beyond the U.S. to make sure that we really get herd immunity on an international basis?

PAUL OFFIT, MD: That is what certainly worries me. You have, through vaccines like

the J&J vaccine or the AstraZeneca vaccine, I mean AstraZeneca was committed to making a worldwide vaccine. They were going to charge roughly $3.40 a dose. They were committed to selling this vaccine inexpensively, which certainly is not Moderna or Pfizer's commitment near as I can tell. And you have 194 countries in this world. I think something like almost 100 of them still haven't given a single dose of vaccine.

You know every year in the United States we give children a polio vaccine, even though we haven't had polio in this country, meaning an American child, just endemic in this country, since the 1970s. I mean it's like, you know, 50 years, we haven't had polio in this country, 40 years. But we still vaccinate against polio because polio still exists in the world, Pakistan and Afghanistan. We are going to be at risk, we are only as strong as the weakest countries out there. So we need to get vaccine out there. And I think that's, if we've put a scarlet letter on these kinds of replication-defective adenovirus vectors with such a rare side effect, I think we're going to do harm.

CRAIG THOMPSON: And how, I think there's also the distribution issues of just the cold chain that you were just mentioning earlier. These vaccines, the single shots, on the viral platform as opposed to the mRNA platform, don't require the cold chain that you just said would be difficult to do in pediatricians' offices in America versus getting it out throughout the world into rural communities, and to all the countries that don't have the advantage of a healthcare system that we have here in the U.S. How are we going to

think about that?

PAUL OFFIT, MD: I agree. I mean I do think part of it is going to be technology does need to be developed to make these vaccines more stable, stable at refrigerator temperature.

CRAIG THOMPSON: Is that possible?

PAUL OFFIT, MD: Sure. I think it's possible. I think Pfizer is actually going to be coming out, I have heard relatively soon with a vaccine that doesn't require this sort of super-cold transfer, meaning -60 to -80 degrees centigrade. That would certainly help. But you're right, we need to vaccinate the world. We do. And our country, which is a technologically and economically advanced country, I'm glad that the Biden administration once again formed a, joined a consortium with the World Health Organization to try and rid this virus from the world. We have a responsibility to the world. And it's not necessarily altruistic, I mean it's selfish in the sense that the degree to which other countries are at risk for this virus is the degree to which we're at risk for this virus.

CRAIG THOMPSON: And then, as you've mentioned earlier, there are now, every country where it's been well studied, there are new variants of Covid-19 that are

appearing. What does that mean for the existing vaccines? Are we going to need boosters? Are we going to need additional vaccines developed? What's that process going to be like?

PAUL OFFIT, MD: So when I think of the word booster, what I think is that the immunity with the vaccines that we've gotten have faded, that the vaccines still work, but the level of neutralizing antibodies, the frequency of memory, cellular immune responses like B and T cells, has dropped to the level that you need a booster. And we have a number of vaccines in pediatrics obviously and in the adult world where we give boosters. So that's one reason to get a booster. We'll find out. I think over the next year or two we're going to find out how long immunity lasts.

Regarding the variants, I should probably take a step back. The virus that started in Wuhan is really not the virus that left China. The virus that left China was the first variant. It was a more contagious form of that Wuhan virus. It was called D614G. And that's really the vaccine, the vaccines are really all designed to protect against that variant. That's the variant that swept across Europe. That's the variant that swept across this country. That's the variant that killed more than 500,000 people. So all the vaccines are made to protect that.

Now the variant, there are variants like the B117 variant that are fully susceptible to the

vaccine that we've given people. So even though it's a more contagious virus, that U.K. variant, it is susceptible to immunity. So that's good. But there are other variants like the South African variant, the Brazilian variant, one of the New York variants, the California variant that are less susceptible to immunity induced by natural infection or immunization. Nonetheless, they're still susceptible enough to prevent severe, critical disease, meaning to keep you out of the hospital, to keep you out of the ICU, and to keep you out of the morgue. That's good.

So that line hasn't been crossed yet. When that line is crossed, where despite natural infection, where despite immunization, you still are hospitalized or killed by a variant strain that is dramatically different and now has escaped recognition by your immune response, then you're talking about a second-generation vaccine. That's not really a booster. That's a different vaccine that you're trying to get out there.

CRAIG THOMPSON: Will that have to go through the same regulatory process? For example, we get a new flu vaccine every year. Flu changes all the time in the way that you're talking about and we don't go through the same regulatory process. Will there be a shortened regulatory process or are we going to have to go through that year mad-dash of developing this new vaccine that might be needed?

PAUL OFFIT, MD: Yes. I mean I would imagine the variants would not be common

enough that would enable you to do a kind of Phase 3 trial. I mean we don't do Phase 3 trials, for example, for meningococcal vaccine, you know, the meningococcus, the bacteria that causes meningitis, because we have maybe 300 cases a year in the United States. So we base that on immune responses. Are we inducing an immune response that's protective? I think that's what would be, would happen here. I don't see it as being a typical Phase 3 trial.

CRAIG THOMPSON: Great. Well, Paul, we're coming to the end of this time. I want to take the opportunity to ask you some questions because I've got one of the world's vaccine experts here. You've been a leading voice, Paul, in addressing the anti-vaxxer movement. And if the audiences are interested, I urge them to read any of the books that you have written on these issues. But I would like to ask you about one area of general concern at the end of this interview. And that seems that you're advocating, as we've heard throughout this virus chat, that every year there are going to be new vaccines and we're going to be urged to take them to solve some of the world's health problems, but that's got parents concerned. Is there an end to how many vaccines we can take? Is there a limit to how many vaccines we can or should take in any period of time or in our lifetime? What are the thoughts about that?

PAUL OFFIT, MD: So as long as there are viruses or bacteria that cause children to suffer or be hospitalized or die, and as long as we can make vaccines that fit into the

schedule and are safe and effective, as long as we can prevent those infections safely and effectively, then we should prevent them. I mean certainly the roughly 14 different diseases that we prevent in the first few years of life or the three additional diseases we prevent in adolescents are a drop in the ocean of what children typically encounter and manage all the time. I mean you have more than 100 different rhinovirus serotypes. You have more than 90 different adenovirus serotypes. There's a lot of viruses out there. I mean even if we take care of the ones that we're currently taking care of, there's still plenty of things that infect children out there. I think as long as we can make them safely and effectively we should do it. We're certainly not overwhelming their immune system. That's not going to happen.

CRAIG THOMPSON: So that's not a concern. So I want to take you back to an example that you just gave us which is the concern that once we start this vaccination, we never stop. You mentioned polio. Many people on this call remember when they got their first polio shot. We haven't had a case of polio in 30 years in the United States, over 30 years and yet we still vaccinate every kid with polio every year. And you just argued that we still do that. But I want people to know that you don't always advocate for continued vaccines as we wipe out the world's pathogens. You advocated 20 years ago at the height of bioterrorism that we shouldn't re-instigate smallpox vaccinations. How did you come to that conclusion and how should we think about that?

PAUL OFFIT, MD: Right. So I was a voting member of the Advisory Committee for Immunization Practices when there was a fear by the George W. Bush White House that smallpox would be used as a weapon of bioterror. We were on the verge of attacking Iraq and they were worried that that would be, either a rogue nation or group would attack us with smallpox. So they wanted us to recommend a smallpox vaccine for frontline responders, you know, EMT people, people who work in emergency departments, etc. I thought that was a bad idea for a number of reasons.

One, we haven't had smallpox in this country since, like for decades, and so we hadn't had a case of smallpox in this country for a long time, also I think in the 1970s. I think the last case of smallpox in the world was like, well, in any case, for decades. Secondly, smallpox is actually a vaccine that can be given post-exposure. It still works post-exposure. So even if you're exposed to the virus, you still can get an effective vaccine.

Three, you know, it's really spread by large droplets, not small droplets, so you need to be within five feet of somebody who is evidently infected with smallpox. There's no such thing as asymptomatic smallpox. If you have smallpox and you have blisters on your face, it's the blisters that break in your mouth that form this aerosol that causes you to get smallpox. So you would know.

And then fourthly, that is not, that vaccine has some, a challenging side effect profile,

that's the nicest way I can say that. I mean, you know, it can cause pretty significant illness, including myocarditis, which is inflammation of the heart, pericarditis, which is inflammation of the tissue that surrounds the heart. Smallpox vaccine was made, when we were talking about this in the early 2000s, with all the technology that was available in 1796. So we can make a better smallpox vaccine. We just didn't make it.

So I voted against that. I was, as it turns out, the only one who voted against that. I think the lesson that I learned in all that is look up when you vote so you can see, you know, whether you were the only person that did this. I mean as it ended up, I ended up being on 60 Minutes with Dan Rather, you know, like under these sort of lights that made me sweat and I actually started to feel sorry for Richard Nixon after a while. So you've got to be careful, I think, when you make...but I think that was, I do think that was the right thing. It was a very short-lived program, about 40,000 people got that vaccine. There were deaths associated with that vaccine. I think we shouldn't have gone forward with that.

CRAIG THOMPSON: Thank you for pointing out that there are times when we do have to evaluate the risk-benefit relative to the disease it causes. We really want to thank you for sharing your passion and your expertise and devoting your time and efforts to infectious disease research and vaccine development. I just want to ask one last human-interest question before I turn it over to Barbara. You grew up in Baltimore. You

were the first in your family to go into medicine. You went to medical school at the University of Maryland-Baltimore. You then took clinical training as a pediatrician. How did you end up being one of the world's experts in vaccinology? What chose you to go in this route with this career that you had?

PAUL OFFIT, MD: Well, when I went to Children's Hospital of Philadelphia, I was fortunate enough to have, as our division chief a man named Stan Plotkin, who was the inventor of the rubella vaccine, you know, the vaccine that prevented the 20,000 cases of birth defects every year. I mean he was a significant contributor to the rabies vaccine. He obviously, we all worked together on the rotavirus vaccine. I was just lucky. And also I became very good friends with, when Merck took up our vaccine and wanted to make it, with a guy named Maurice Hilleman, who was the father of modern vaccines. He did the primary research and development of nine of the fourteen vaccines we currently give to infants and young children. So I was just lucky. I mean I was around people who just knew this and were good at it. I was in the right place at the right time.

CRAIG THOMPSON: Well, Paul, thank you on behalf of all of us that have been listening for carrying on in that tradition. I should point out you are the Hilleman Professor at the University of Pennsylvania and Children's Hospital of Philadelphia in recognition for your contributions. Thank you for taking time with us, and I'll turn it back over to Barbara.

PRESIDENT BARBARA VAN ALLEN: Thank you so much, both of you, Paul and Craig. What an amazing conversation, terrific insights, and we really appreciate it. We know you can both be in a lot of different places at this moment, so thank you for sharing a little bit of your time this afternoon.

I'm pleased to report that we have many great speakers coming up. And as always, we encourage you to invite guests. We have John Waldron, the President and COO of Goldman Sachs on Monday, the 26th followed by Robert Swan, the polar explorer, and he'll be talking about climate change and the impact on the poles on April, the 28th. We have Ben Hecht, the President and CEO of Living Cities on the 29th. Dambisa Moyo, the Co-Principal of Versaca Investments and author, speaking on her new book on May 4. And then we are going to begin sitting down with the top candidates for the New York City Mayor. And we've gotten confirmations from Eric Adams for May, the 6th, and Ray McGuire, May, the 10th. So stay tuned for more announcements on that. We also have Henry Louis Gates, the popular PBS series host and historian, Alphonse Fletcher University Professor and Director of the Hutchins Center for African & African American Research at Harvard University on May, the 11th. So we have many more to come. If you're interested in membership, by the way, do let us know.

And finally, just a quick thank you to those members of the Centennial Society joining us today as their contributions continue to provide the financial backbone of support for the

Club. Thank you and please all stay healthy, stay safe, consider getting that vaccine.

Thank you.