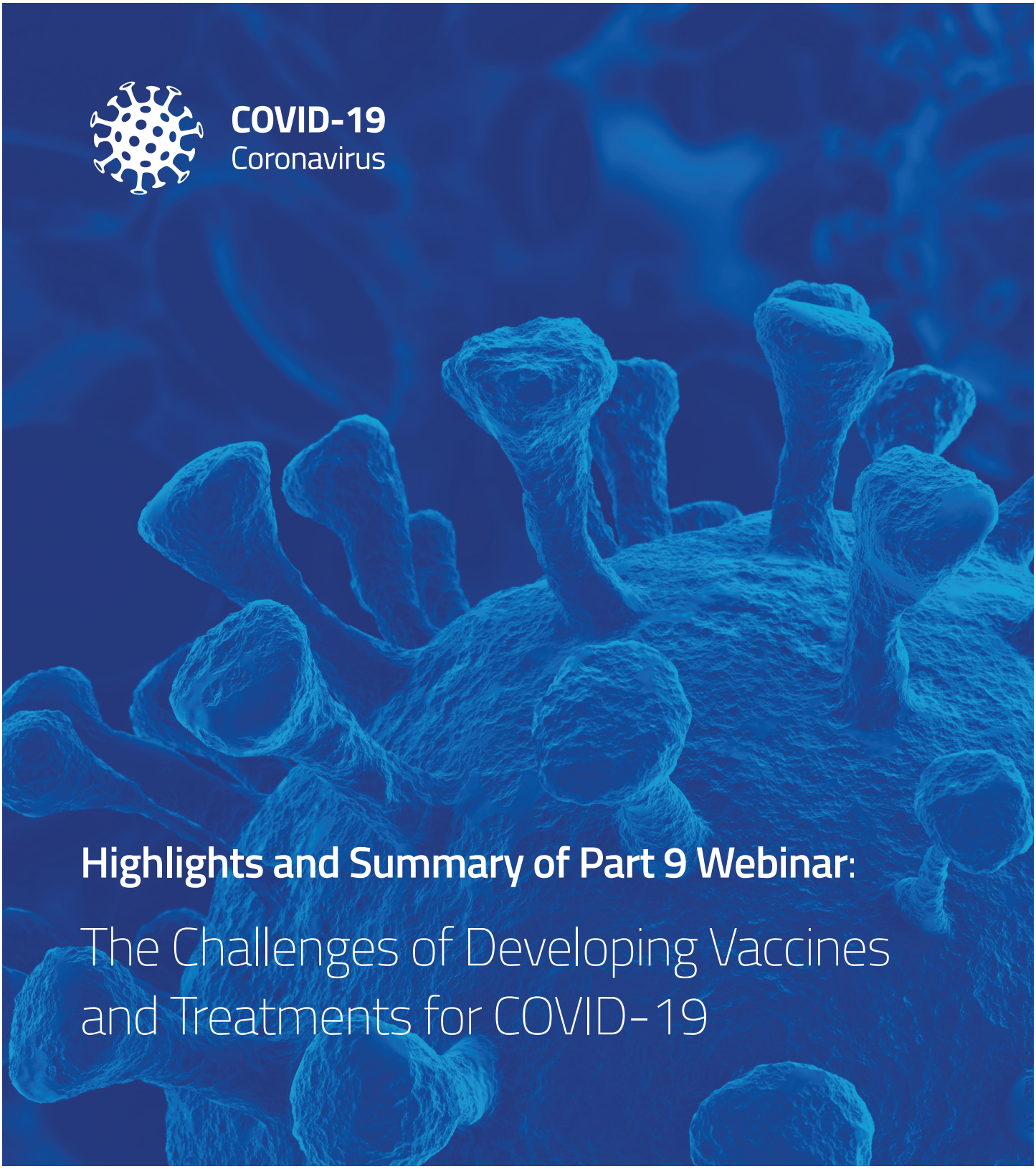


Highlights and Summary of Part 9 Webinar:

The Challenges of Developing Vaccines and Treatments for COVID-19

wcg™

The May 13 webinar focused on the development of vaccines and treatments for COVID-19. It begins by looking at the remdesivir development pathway and Gilead's experience of designing and conducting clinical trials in a brand-new disease without the benefit of medical guidance or regulatory precedent. Then we move to a discussion of vaccines, looking at the realistic timelines and the ethics of human challenge trials.

Featured speakers:

1 **Anu Osinusi, MD, MPH**
Executive Director of Clinical Research, Emerging and Respiratory Viruses, Gilead Sciences

2 **Arthur Caplan, PhD**
Professor of Bioethics, NYU Langone Medical Center

Lindsay McNair, MD, MPH, MSB, *Chief Medical Officer, WCG,* moderated.

This is the ninth in **a series of WCG webinars** that address the coronavirus-related challenges facing the clinical trial industry. You can find links to this webinar and an array of COVID-19 resources on our **WCG Insights Program** page.

Looking at the Remdesivir Journey

1

Anu Osinusi, MD, MPH
Executive Director of Clinical Research, Emerging and Respiratory Viruses, Gilead Sciences

Remdesivir Timeline

A timeline helps put the development of remdesivir in context.

December 2019:
Learning about "mystery pneumonia" cases in China.

Early January 2020:
Novel coronavirus first identified by the Chinese CDC.

Mid-January:
- WHO declares a global health emergency.
- First case of human-to-human transmission in the U.S.
- Six cases total in the U.S.

February:
Three clinical trials launch.
- First two remdesivir trials begin in China: One for mild to moderate COVID-19 and one for severe COVID-19. (At that point, 99.9% of the cases were in China.)
- Later that month, Gilead collaborated with the National Institute of Allergy and Infectious Diseases (NIAID) on a trial.

All three trials were double-blind, placebo-controlled, randomized studies.

March:
- WHO declares a pandemic.
- Global cases: roughly 118,000; 2,400+ deaths.
- U.S. cases: 1206; 40 deaths.

April:
Global infections top 1 million

May 13:
- U.S. cases: 1.4+ million; 82,000+ deaths.
- Global cases: 4+ million; 250,000+ deaths.

Rationale for Remdesivir Use for COVID-19

At the start of January, what we knew about remdesivir was...

Nonclinical: The virus at that time was not even identified; a couple of things coming out of China suggested similarity to SARS.
- Virus homology showed significant similarity to SARS (96% sequence homology in polymerase gene).

- Remdesivir had demonstrated potent in-vitro and in-vivo activity against other coronaviruses (SARS and MERS).

Clinical: This drug was already being evaluated for Ebola in the Democratic Republic of the Congo. So there was already a database of individuals with acute Ebola virus as well as healthy volunteers and some who had the coronavirus disease, but we had no information about the new virus itself.

The situation: A new virus for which no drug had proven safe or effective. There was some safety data in a different population. And the cases were rapidly escalating across the globe.

So the first question to answer was:

Is remdesivir a safe and effective treatment for COVID-19 patients?

The first three trials addressed that question.

- The first China study looked at a population with severe COVID-19: It was underpowered and discontinued due to low enrollment. The data were available, but inconclusive. *(Published in LANCET)*
- The second China study, of a moderate population, enrolled only about a quarter of its target. It has been suspended.
- The NIAID study, fully (far beyond the initial target sample size) enrolled 1,053 patients with moderate, severe and critical COVID-19. It demonstrated efficacy, and the top line result was released to the public. *(NIH Press Release April 29)*

Question 2:

Is a 5-day treatment course as effective as a 10-day course?

- The Gilead study in the severe population shows similar 5-day/10-day efficacy in patients who are not intubated. *(Preliminary data in Gilead Press Release April 29)*
- Another Gilead study, in the moderate patients, is in progress (as of May 13th). The readout is expected in the next few weeks.

So why the duration of treatment question? When you look at respiratory virus drug development, a lot of times the treatment is five days or less. Therefore, it was important to study that in COVID.

Trial Considerations

Key considerations in the remdesivir trials included:

- Which populations should be studied first?
- Which endpoints are clinically meaningful?
- What is the utility of viral load testing? With COVID, we didn't really know how long viral shedding persists and how much that might drive some of the outcomes. We know now it's much longer than what you see with flu or some of other respiratory viruses.

Other considerations:

- Heterogeneity in clinical practice and management: Practice is very different in different centers.
- Logistic challenges facing all in a global shutdown:

- Hospital restrictions of non-essential personnel
- Training, SIVs, monitoring visits performed remotely
- Stretched site personnel pulled into clinical duties
- Shortage of testing supplies

Compassionate Use and Pre-approval Access

Should a Compassionate Use program exist pre-proof of concept? Typically, you have proof of concepts before you have a Compassionate Use program, but this was a disease with no treatments at that point. And at that point, there were only nonclinical data and clinical trials that hadn't read out. And there were sick patients.

What is the ethical and responsible thing to do in that scenario? Here is how it played out.

January 2020:
First two Compassionate Use requests: U.S. and France.

February 2020:
115 requests received.

March 2020:
More than 300 requests a day from over 20 countries.

Within a six-week period, Gilead shipped medication to 1,700+ patients through the Compassionate Use program.

There's a lot of regulatory paperwork that needs to happen, so it's a very labor-intensive process. Gilead was overwhelmed by demand, leading to delays. Travel restrictions led to additional delays with the shipping. So, recognizing Compassionate Use was not meeting the goal of getting drugs to patients as quickly as possible…

March 2020:
Gilead put in place an expanded-access program. The Compassionate Use program continued for pregnant women and pediatric patients.

May 1:
FDA announces emergency use authorization, which improves access for patients beyond Compassionate Use and expanded access.

Which Endpoints are Clinically Meaningful?

Some people have had questions about the endpoints selected for each of the trials. It's important to note that when all these trials started, in January or early February, there was very little known about the natural clinical course of COVID-19. But that changed as more data was collected.

So you go back and look at your endpoints to see if you are missing something. Which endpoints are clinically meaningful? Which endpoints can physicians look at and have an idea of what works?

Primary endpoints for seven clinical trials for treatment of COVID-19 included:

- Time to clinical improvement by Day 28

- Time to clinical recovery by Day 28
- Time to recovery on 8-point ordinal scale
- Clinical status at Day 14 on 7-point ordinal scale
- Clinical status at Day 11 on 7-point ordinal scale
- Clinical status at Day 15 based on 7-point ordinal scale
- In-hospital mortality [Timeframe: 3 weeks]

When you look at all these different endpoints, it's really just an approach to try to figure out what's most clinically meaningful as more information about COVID-19 becomes available.

- You want to look at the measurement that works best for outcome evaluation, which is probably dependent on disease severity.
- You also want to look at outcomes that are easily interpretable and capture how patients function or feel or survive.
- You want an outcome that leads to efficient evaluation of the treatment efficacy.

Utility of Viral Load Testing

- WHO guidance states a greater understanding of viral dynamics in COVID-19 is needed to optimize timing and type of clinical material used for testing.
- Results may vary depending on assay used, specimen collection site, specimen quality, timing in illness, and mutations.
- More research is needed to understand the following:
    - Optimal timing and type of clinical material to sample
    - The relationship between viral concentration and disease severity
    - The duration of shedding, and relation to clinical picture (e.g., clinical recovery occurs with viral clearing, or shedding persists despite clinical improvement): We see all these reports of people who recovered, but they're still spreading the virus afterward. What does that really mean?
    - Utility of viral load monitoring in upper versus lower respiratory tract
- Other issues include testing-supply shortages and concerns about risk to healthcare workers.

Evidence Generation

The scope of this pandemic has led to extensive global evidence generation—not only for the remdesivir program but across different programs, the Vaccine Networks or other therapeutics. It's just led to really extensive global evidence generation. You look on clinical trials.gov and see all the trials being conducted. COVID-19 has spurred a lot of ingenuity as to how we do these trials and keep them simple so you can get answers as quickly as possible. It's also influenced how we do things at the manufacturing level.

There are a lot of studies ongoing with remdesivir, and some of those are going to be extremely helpful as sources of data and to shake out some of the really important questions as well.

That leads to the final question:
Can we do better? Are there combination strategies we should be thinking about and working towards with other targets to ensure that we can even improve on these outcomes we're seeing from these ongoing studies?

Vaccine Development and Human Challenge Studies

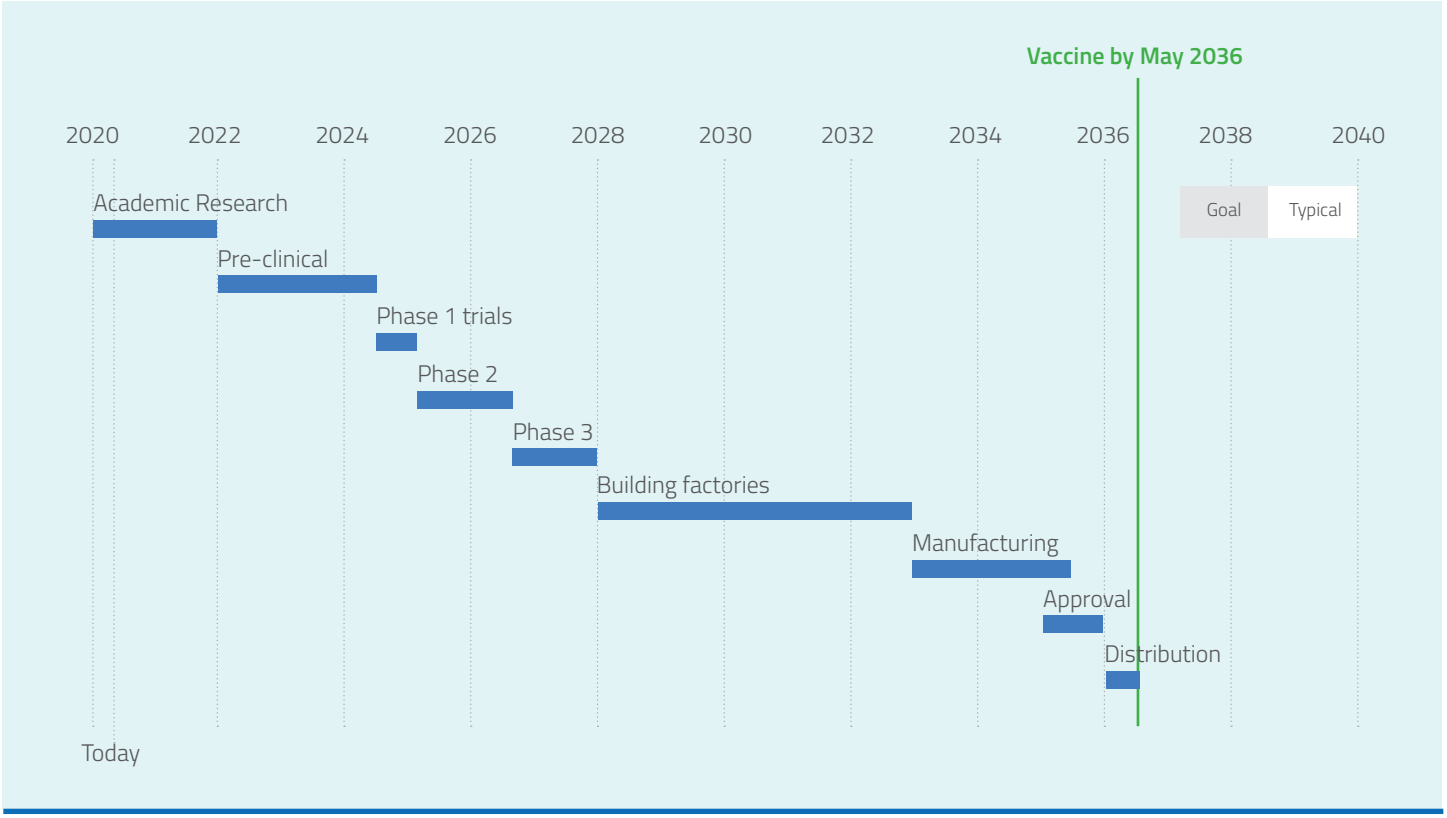
2 Arthur Caplan, PhD

Professor of Bioethics, NYU Langone Medical Center

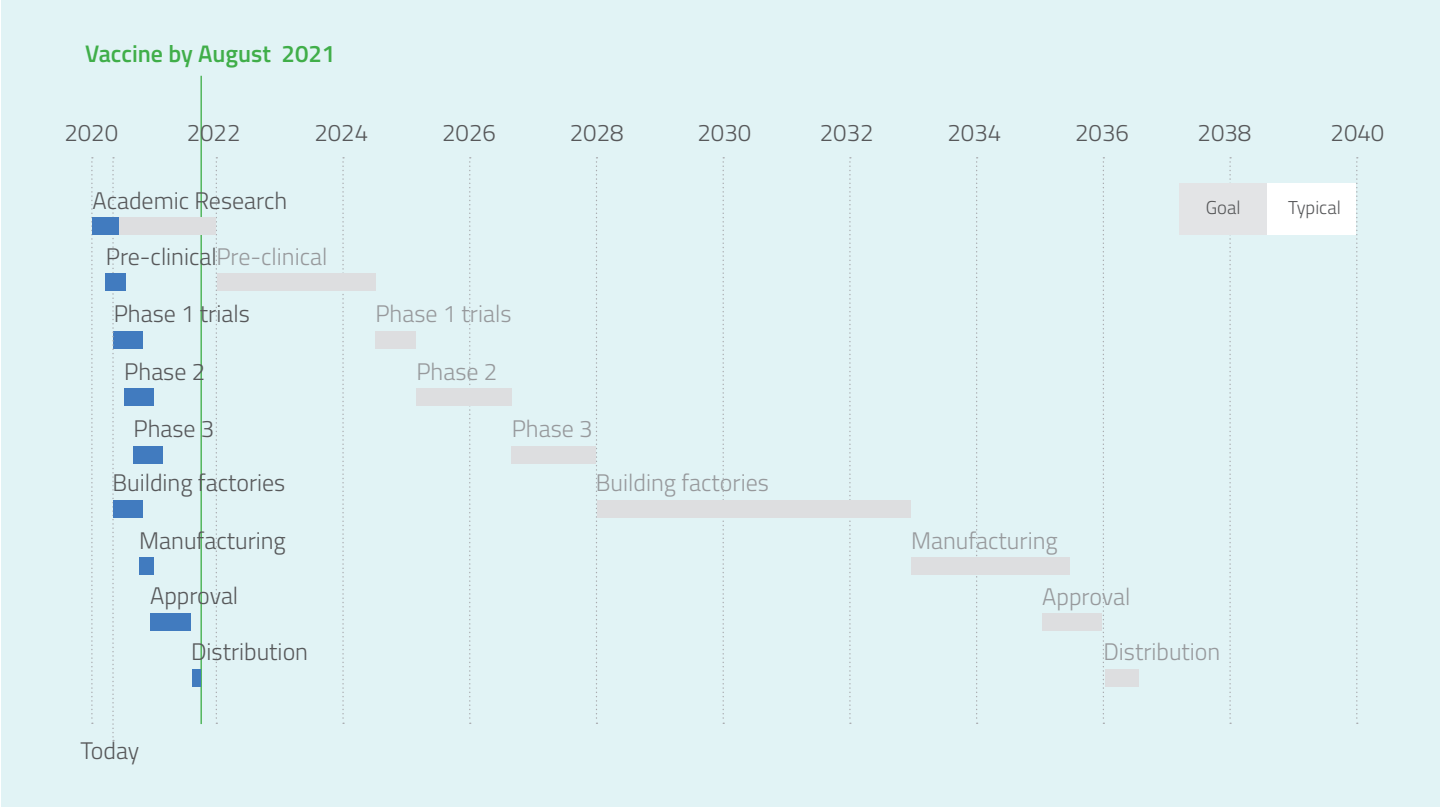
Note: The views and opinions expressed in this portion of the presentation are those of Arthur Caplan, PhD, and should not be considered WCG positions or policy.

Many organizations have vaccine development programs underway. Nine have advanced to human clinical trials. Over 100 companies are trying to produce vaccines. We've never had 100 companies working at the same time on a single disease. "That said, the goal of having a vaccine available quickly is one that I'm going to say, I'm afraid, I don't think is going to happen." The usual timeline for getting a vaccine developed is closer to 15 to 20 years. The fastest vaccine has been six years. And let's remember, we've been hunting for an AIDS vaccine for about 30 years and we haven't found one.

Typical vaccine development timeline...



vs. COVID-19 vaccine target timeline...



(Source for both timelines: "How Long Will A Vaccine Really Take?" *New York Times* Opinion, Stuart A. Thompson, April 30, 2020)

There are other reasons to be skeptical that a vaccine will arrive in the fall, or six months, or 12 months, or even 18 months. Even if you find an agent that works, there are many obstacles to overcome:

Manufacturing challenges: Even if you found a vaccine, you have to manufacture it in huge amounts. This is no small undertaking. It must be done very carefully. These are vaccines that would be potentially produced in the billions of doses. This is no small activity.

Efficacy: Many–if not all–vaccines are less than 100% effective. Mumps vaccine is about 80% effective; rubella, about 93%; whooping cough, about 75%. The flu vaccine is only 40% to 60% effective. You're going to face trouble for still big numbers of people who won't be immune.

The need for multiple shots: The HPV vaccine for cervical cancer is a two- or three-shot vaccine. The flu shot is annual. Cholera is a multiple-dose vaccine. If this vaccine requires more than one shot, there will be staggering manufacturing and distribution issues.

Distribution: This will turn out to be a battle, as we've seen with remdesivir, in terms of who's getting it and where. The U.S. and the U.K. have already said that if they're investing in vaccines, they're going to use them first in their own country. Other countries are likely to do the same. WHO insists that vaccines ought to be available where they're needed the most. Expect a lot of battling about where the initial batches of vaccine go. That could set off quite an international dispute at a time when people are already panicking about this plague.

Cost will be an issue. No one said the vaccine would be cheap to make. That is going to drive a lot of problems in terms of gaining access everywhere around the world, presuming you don't want to create pockets where people are not vaccinated and the virus can incubate and come back and get us later.

Safety: Deciding how much we're going to tolerate in the way of risk.

Time: As mentioned earlier, it takes a long time to develop a vaccine. And one of the major reasons it takes a long time is, we start with animals and then move to human volunteers just to be vaccinated, to see what happens. Then we vaccinate large numbers of people. And we send thousands of people back out into the world to wait for nature to infect them, to see whether they are protected, or whether they suffer adverse events.

You're waiting for natural infection to get an answer, both about safety and efficacy. If you're waiting for people to get naturally infected, to see what's going to happen, and the virus ebbs and flows, you could be waiting a long time to see a result. Either about safety or about efficacy.

Population: It's unlikely that high-risk people, such as elderly or immuno-compromised people will participate in the trials.

So, what is the alternative? Insert human challenge studies.

Human Challenge Studies

In challenge studies, instead of waiting for nature to infect people slowly and accumulate data, you deliberately infect someone with the disease. You immunize a much smaller group of people, say 500 to 1,000. And then you study them to see what happens after you administered the disease.

Administering the disease, to put it mildly, is ethically controversial. Is it worth taking the risk compromising subjects, to deliberately give them a disease?

This plague is killing so many people. If we wait a couple of years for natural infection there'll be many, many deaths occurring all over the world while we're waiting.

- Fewer study participants are needed because the "unprotected" infection rate will be so high, it's easier to see a difference.
- Faster to conduct because the infections happen immediately in the controlled setting, rather than in the general community.
- Fewer people at risk.

"I think the stakes are so high. The impact on the world is so huge. That morally, what I might normally say is not defensible, I think becomes defensible."

So if it is defensible, certain conditions would have to be put in place.

- **Select subjects you think are least likely to become ill** from anything that the COVID virus might do. That would be healthy adults, probably 20 to 29. The risk of death in that group, and hospitalization, is extremely small.
- **No coercion:** Participants must freely and voluntarily choose. They must understand what's known, and what isn't known, and what could really go wrong.

  That probably means not paying them: You don't want anybody doing it for any reason, other than altruistically trying to help the world get out of this box.

A challenge study could shave six months to a year or two off the time it would take to study one vaccine. But remember, the first vaccine may not work. Human challenge studies would speed the process if we had to go through many candidates to find one that actually was effective enough and safe enough.

No Room for Error

In many parts of the world, people are wary of vaccines. Whether we use a challenge study or standard methods, if something goes wrong and participants get sick from the vaccine, many in the public would not support another vaccination. **Meaning you get one chance at this.**

Questions from Audience

Questions for Osinusi

Anu Osinusi, MD, MPH
Executive Director of Clinical Research, Emerging and Respiratory Viruses, Gilead Sciences

&

Questions for Caplan

Arthur Caplan, PhD
Professor of Bioethics, NYU Langone Medical Center

Q **So, Anu, there were some questions about control groups and standard of care for COVID-19. What would be considered standard of care, given that no one had approved drugs for this area? There were also questions about the use of placebos. There was probably not a large supply of remdesivir-matching placebo sitting on a shelf, waiting to be used. Did the availability of placebo and the time it might take to be able to generate matching placebo, have any impact on how you designed your studies?**

A **Osinusi:** I would say yes and no, to an extent. Going into this in January, we had some matching placebo leftover from the Ebola program. Essentially all that went to the first three trials–the two studies in China and the NIAID.

But the most important this thing is to divert your manufacturing efforts to manufacture active drugs. And of course, down the line if you needed more placebo, you could manufacture it then.

We didn't have enough matching placebo. As the NIH study size increased over time, there were sites in Europe that didn't use the matched placebo. They use another placebo that was labeled so it was not obviously a placebo.

You asked about standard of care. Everyone received supportive care as per the standard of care for that hospital site. A lot of sites early on in Asia had Kaletra (lopinavir/ritonavir) as the standard of care.

And then once that ran out, that changed. So, whatever the standard of care was at that site, at the study site hospital, was what I meant by the standard of care.

McNair: Thank you, Anu. I should also clarify, because we had a couple of questions come in related to this, with not just the remdesivir studies, but many other being conducted in sick patients with COVID-19. When we refer to placebo-controlled studies, we're not talking about the people in the control arm getting nothing except placebo. We're really talking about people getting the best supportive care in both arms. And then in one arm getting remdesivir or the investigational agent, and the other arm getting blinded placebo, on top of that baseline of best supportive care. So even though we refer to placebo-controlled, it would not be approvable or ethical in any circumstance to do studies in sick patients like this, and to say, "We are giving you no treatment except placebo treatments."

Osinusi: Yes. It's additional treatments on top of the best supportive care.

McNair: All of us in clinical research should probably talk about it as placebo-blinded rather than placebo-controlled, because the control is really standard care–best supportive care. But they are blinded with placebo.

Q **Art, how do we square the risks of human challenge studies in a younger population to develop a vaccine that may be most urgently needed in a different segment of the population?**

A **Caplan:** Remember, even in standard trials, it's unlikely we're going to see people recruiting older or nursing home residents. I think it's a problem we're going to have no matter what method of research we do. If we do conduct human challenge studies, they'll be in younger people. If we do standard clinical recruitment, the likelihood is we're not going to see many people recruited in over 65, because the scientists will be skeptical about seeing an effective response in that group anyway. So, it's probably a gradual rollout, once you establish safety and efficacy, whichever way you do it, to then see whether it does help the older population. And I think they're going to be involved, but they're going to come later.

Q **Anu, you had talked about how, by the middle of May, you were getting 300 requests a day for Compassionate Use. What did the team look like within Gilead? How many people did you have assigned to that project?**

A

Osinusi: A lot, to put it lightly. It was a significant number of people because, I think, the teams just came together recognizing that when you get a request in, that's someone at the other end, right? That's a patient in a hospital that a physician is asking for. So, whatever we need to do, we need to get it done. So we had teams within the U.S. and teams in Europe, so that there was no lag time.

But, it was a significant number of individuals involved in those efforts to make sure that we could get it done as quickly as possible. But even with that, individual patient Compassionate Use is not meant to be able to meet that type of demand in any setting.

McNair: As you said, single-patient Compassionate Use is not meant to be a scalable system. It's meant to be for one-offs. I should probably also mention just for complete disclosure, that for the large-population expanded-access program that Gilead does have going on with the remdesivir program, we, Western IRB, are the single IRB for that program.

Q

Art, you are very involved in a lot of the discussions around COVID-19 treatment and vaccine development. You're talking to a lot of people that are very involved in this effort. Are you seeing more collaboration among companies, companies and institutions, organizations, than you have before in other settings?

A

Caplan: The answer is yes. You're seeing many, many more multicenter sites organize very quickly to speed answers to questions about the impact of various drugs.

At NYU, where I am, I know many of our researchers are working on everything from plasma to antivirals, to interleukins, with other groups in ways that just didn't happen that fast, if at all, before. So that's been important, and I think is a thing that–I hope–carries through past the COVID plague.

Vaccine-wise, there are many, many platform studies. WHO has organized a big multi-sponsor activity. There's the Warp Speed project here, and the ACTIV project, which some will read about later in the newspapers. In one instance, there's a common placebo group, so everybody doesn't have to find a group to act as the control arm, if you're doing a standard study.

So, absolutely yes. It's a good thing. It's a positive outcome, I think, from some bad circumstances.