

1 in a high percentage, up to almost 90 percent of
2 subjects. That could be boosted by a second
3 immunization, leading then to seroconversion rates
4 close to 100 percent. And already in phase one, an
5 urgent question that may be on the mind of some people
6 here and that certainly was on my mind when I first
7 heard about the technology and that they're ripping us
8 all the time is how in the world can this work in the
9 population that all has, or many of us has -- all of us
10 should have received the measles vaccine at some point
11 in their life and may have measles antibodies? So this
12 was largely addressed in phase one and, as I will show
13 you in a second, also in phase two by grouping the
14 subjects into groups of varying levels of preexisting
15 measles antibodies.

16 So you have the quarter with the lowest,
17 middle and so on, and then the highest. And that's in
18 the lower panel here. Oops. Of course. Here we go.
19 It's a little bit of an awkward angle here. Yeah. And
20 you can see there's actually no correlation whatsoever
21 between the level of preexisting antibody and the

1 chikungunya antibody response after vaccination. Many
2 people have found that very surprising. It was
3 repeated in phase two. I actually don't have it here
4 on this slide, but it is a very similar panel just with
5 a much larger number of patients. And Themis was very
6 brave in phase two and even included an arm that was
7 immunized with measles a month before they received the
8 measles-chikungunya vaccine. And even there, this is
9 published data. There was no influence whatsoever. So
10 apparently, this is not a problem for this particular
11 vector.

12 Otherwise, phase two repeated what we have
13 seen in phase one, seroconversion rates of almost 90
14 percent after one, almost 100 percent after two
15 vaccinations and the ability to boost with a second
16 shot. The excellent immunogenicity data also supports
17 progression to a clinical phase three and licensure. I
18 would also like to mention that this program has been
19 extensively looked at and validated by regulatory
20 agencies. There have been clinical trial applications
21 being approved in several European countries and also

1 by the FDA in the U.S.A.

2 The development program is currently under
3 discussion with both the FDA and EMA. And due to the
4 urgent medical need, both Europe and the FDA in the
5 U.S. have awarded the PRIME and Fast Track designation
6 respectively. Actually, we are proud to say that we
7 were the first company to have both of those
8 designations awarded.

9 So considerations for licensure, some of this
10 is repetitive, but let me still also give our point of
11 view. Of course the traditional approval route would
12 be through a randomized controlled efficacy trial, and
13 we would all like to do that, if that were possible.
14 Like other people, we've intensely looked at the
15 existing epidemiology data. We've had conversations
16 with health officials in countries also like Brazil
17 where we met the Minister of Health for the state of
18 Rio de Janeiro. We've talked to epidemiologist in the
19 U.S. and Europe, all over the world, and have come to
20 the very clear conclusion -- and we will talk about
21 this a little bit more in detail -- that a traditional

1 randomized controlled efficacy trial is not feasible,
2 given the specifics of the epidemiology of chikungunya.

3 A human challenge trial might also be an
4 interesting thing to do, but there is no established
5 challenge virus and human challenge model. And we
6 would think it's also probably a very long shot and not
7 easy to establish one given the peculiar
8 pathophysiology of chikungunya and the theoretical
9 concern that also an attenuated virus might cause some
10 long-term sequelae. So that leaves us with the
11 protocol.

12 Fortunately, there exists an accelerated
13 approval based on a surrogate endpoint. And as has
14 been so nicely and clearly already pointed out by the
15 previous speakers, this really looks good in the case
16 of chikungunya because there is ample evidence that
17 neutralizing antibodies can serve as such an
18 immunological marker to predict protection. Just to
19 talk about this, what I envision the challenges for the
20 randomized trial was -- the epidemiology is, and we
21 have seen that it's pretty typical, actually, for some

1 of those emerging (inaudible) viruses. If it reaches a
2 new population, you get a massive outbreak. It sweeps
3 over the country, and then what's left is kind of a low
4 but still ongoing activity of sporadic cases. And then
5 you have those flares that pop up here and there that
6 so far nobody has been able to predict where they will
7 happen and that are usually short-lived, usually not
8 longer than a year or less than a year.

9 And somebody who knows how to setup a phase
10 three clinical trial would say a year is usually what
11 you need to set up a clinical trial. So at the moment,
12 you detect a flare. If you start setting up, you will
13 certainly be too late. So that certainly will not
14 work. You were to rely on extremely good surveillance
15 data. In spite of efforts, as we've heard today,
16 surveillance is becoming better. Nevertheless, it's
17 also not easy because you need serological
18 confirmation. You need PCR confirmation. That doesn't
19 happen. And many of those outbreaks, we've actually
20 only detected in retrospect and not in advance where we
21 could still react with a clinical trial. And then, of

1 course, also the infrastructure would have to be
2 excellent, which the reality of the world is not too
3 pursue such a trial in a short timeframe.

4 So for all of these reasons, we feel that it
5 is not feasible to do such a randomized controlled
6 trial for the licensure of chikungunya. Just as an
7 example, we've done the mathematics for many regions.
8 I'm showing you here the example using the current
9 incidence rate of Brazil where you could make a back of
10 the envelope calculation of a viable sample size of
11 more than 100,000 to have the right number of cases.
12 And even that, of course, assumes that there is not a
13 major change in the epidemiology during the time that
14 you are making -- you see that there are certain spots,
15 here, for instance, in Brazil, where you have higher
16 attack rates. But it's very clear that those spots
17 will not be the same in a year or two from now when a
18 trial might start. They will wander around, and it
19 will be very difficult to follow those.

20 Calculations with other countries, like
21 Thailand, gave even higher numbers. The new

1 epidemiology that comes up now, of course, needs to be
2 assessed. And that may be very useful for post-
3 licensure effectiveness trials, and I will talk about
4 that in a minute. It will very certainly be very
5 useful, but in our analysis, we do not find it
6 sufficient for a perspective randomized control trial.

7 So what could the proposed path to licensure
8 look like? We envision it to rest on three pillars: a
9 phase three clinical program already mentioned several
10 times today; fortunately very useful non-human primate
11 model, depending on passive transfer of human
12 antibodies to a non-human primates; and a post-
13 licensure effectiveness program, which, of course, even
14 though the term is post-licensure, has to start already
15 now in its preparations and its set up -- so already in
16 the licensure phase. The phase three clinical program
17 that is actually already in its final stages of
18 starting with first dosing will have the goals of
19 expanding the safety database in our target population
20 of adults 18 years and older, the confirmation of
21 vaccine safety in both endemic and non-endemic

1 populations. The evolution of immunogenicity by
2 measuring and utilizing antibodies is our presupposed
3 correlate of protection and also important the
4 demonstration of a clinical lot to lot consistency.

5 Second pillar, the non-human primate model, we
6 fortunately already heard a lot of good things, and we
7 will hear more in the afternoon. By and large, the
8 non-human primate models are an excellent model for
9 chikungunya infection because they're natural hosts.
10 So we can really replicate the human infection mode,
11 which is a local infection in the skin by a mosquito
12 bit, which you can mimic by an intradermal inoculation,
13 which leads to a first round of local amplification to
14 the lymph nodes, spreads to lymph nodes, lymphatic
15 tissue. From there, it goes into the blood stream
16 viremia, where it then spreads to the organs.

17 So exactly the same thing happens in non-human
18 primates as it happens in humans, and the question is
19 can we interrupt that in the model, in the non-human
20 primate model, using antibodies from vaccinated humans?
21 That is the question that we would like to address in

1 this model. And I don't need to go into the detail of
2 the evidence that suggest strongly that neutralizing
3 antibodies are indeed a useful correlative protection
4 for chikungunya because that was already lined up
5 nicely.

6 We've done our own homework and made a proof
7 of concept study with non-human primates, similar to
8 what we've seem previously. I have to say, as a
9 scientist, when I look at a result like this, I'm
10 always very happy because it's one of those rare
11 results in science where you don't need difficult
12 statistics to really see what's going on. Basically,
13 every single monkey that received naïve, not immunized,
14 serum from humans was infected and developed a high
15 level of viremia. Every monkey that received
16 antibodies from vaccinated humans was fully protected
17 against viremia, so that is a very easy interpretation.
18 And we also looked -- we have heard already about the
19 possibility of showing arthralgia in this model, but we
20 think it's very important to look at the presence of
21 viral RNA in the joints because, to our best

1 understanding, pathology is linked to the -- I know
2 that not the very final word may be spoken here.

3 But all evidence points towards that the
4 pathology is linked to viral invasion of the joint. So
5 if we do not find RNA in the joint, it seems reasonable
6 to conclude that we will also prevent the joint
7 symptoms, at least in the acute phase, which is the
8 phase that we're looking at here in this model. And in
9 fact, that happened. Although, we could totally
10 prevent invasion of the joint. And we found RNA in
11 every single joint that we looked at in this particular
12 experiment of those monkeys that got infected because
13 they had received naïve serum.

14 Not only that, but also in this model it
15 became clear that the immunity transferred by the human
16 serum from vaccinated people was sterilizing in that
17 model, measured as effected the non-protected animals
18 developed high -- strong immune response and the high
19 titer after challenge because they were infected.
20 Those animals that had received the vaccinated serum
21 pools were not boosted, but this immune response of

1 course was diluted and disappears. And there was no
2 reaction, which would be an indication of a sterilizing
3 immune response. Of course, I use the term sterilizing
4 immune response, quote/unquote, because we never know
5 if it's really sterilized or if it's just a small local
6 replication that didn't lead to an immune response.
7 Note that the titers of those animals that were fully
8 protected was actually quite low, 20, which is in line
9 with the observations that perhaps a titer that is ten
10 or higher is already fully protective.

11 Now, of course, this will have to be done with
12 a series of various titers and then apply a
13 mathematical model to really detect the threshold of
14 protection to fully define the correlative protection.
15 But this experiment certainly suggests that that
16 threshold will not be higher than 20 but probably
17 lower, perhaps in the region of ten. But that still
18 remains to be done.

19 Important question is always what makes us
20 confident that we can bridge those animal data to the
21 human citation? I already talked a little bit about

1 the validity of the model, as we see it and as we've
2 heard it also from the experts working in the field,
3 like our presentation this morning. The disease
4 parameters are -- I talked about viremia, fever. I
5 didn't mention invasion of the joint, but of course
6 there's a panel of other blood parameters. And we're
7 still working on information parameters in the joints
8 that can be monitored that allows this translation.

9 As I said, a protective threshold will be
10 determined. And I would like to say a few words about
11 that. There is two different ways to make that
12 experiment. You can purify antibodies from individuals
13 and then transfer single individual's antibody into a
14 monkey. Or you can make pools and use those pools and
15 dilute them. The details of how this will be done at
16 the end are still under discussion within the company
17 and certainly with the regulatory agencies. But let me
18 just say at this point that I think there's pros and
19 cons to both of these things. A pool can be criticized
20 for potentially not taking care of individual
21 variation.

1 On the other hand, I would argue that a
2 vaccine is also made to work in the general population
3 without stratification of who has which HLA type or who
4 makes which kind of functional antibody type so that
5 there's also an advantage of having this normalization
6 that you have in a pool. And using dilutions of a
7 pool, of course, mathematicians like that because that
8 allows you to apply a relatively simple recreation
9 model to calculate the threshold. The individual, of
10 course, has other advantages not having those potential
11 problems arising from pooling and from diluting. So I
12 think at the end of the day it will need a combination
13 of both to satisfy and to make this model really fully
14 translatable. But as I said, details have still to be
15 decided here.

16 Third and last pillar of the path to licensure
17 is the development of a post-licensure effectiveness
18 program. As I've said, this is already ongoing. So
19 continuous engagement with epidemiologists and with
20 authorities in endemic countries is something that
21 Themis is intentionally engaging in. Certainly long-

1 term follow up of clinical phase three participants, as
2 far as they are in endemic countries, will be an
3 important component of that post-licensure
4 effectiveness program. We heard already about
5 potential setup of outbreak intervention protocols of
6 observational case control studies. And I think that
7 data, as we have just heard from Thailand, will be
8 invaluable for developing those -- such protocols and
9 setting up such studies for post-licensure
10 effectiveness programs. Not entirely in the same part,
11 but equally important and still related is that, of
12 course, Themis will seek as quickly as possible WHO
13 pre-qualification because we really feel strongly to
14 make this vaccine available as quickly as possible to
15 people effected in low- and middle-income countries as
16 well.

17 Summary is just to summarize what I said. Our
18 goal is to develop a vaccine for adults in endemic and
19 nonendemic regions of the world. We have observed an
20 excellent safety immunogenicity profile for our
21 candidate vaccine in more than 500 subjects that

1 clearly allow for the initiation of a phase three
2 program, and that is ongoing. We've received extensive
3 regulatory validation in multiple countries, and we
4 have a commercial manufacturing process ready and the
5 proposed path to licensure, as we see it, but of course
6 are awaiting guidance and feedback on this from the
7 committee and from the FDA. If a phase three clinical
8 program, which is being started, then a non-human
9 primate model to demonstrate it because clinical
10 benefit from the variation of immunological marker of
11 protection neutralizing antibodies and the development
12 of a post-licensure effectiveness program.

13 These leaves me with my last slides, which are
14 the acknowledgements. The Themis team cannot be
15 acknowledged enough. They're incredibly efficient.
16 They're still a relatively small team and have done
17 tremendous work. The technology comes from Institute
18 Pasteur. I already mentioned but really want to repeat
19 the support and the invaluable help that we've received
20 from CEPI, SBRI, and particular also from NIH and
21 Walter Reed. It's unbelievable how much that has

1 helped us and how great it has been. And then I chair
2 the scientific advisory board and would also like to
3 acknowledge the advisors in this board and thank you
4 for your attention.

5 **DR. EL SAHLY:** Thank you, Dr. Mandl. I would
6 like to invite now Dr. Wolfgang Bender. He will be
7 giving a presentation on live attenuated chikungunya
8 virus vaccine candidates. Dr. Bender is the chief
9 medical officer at Valneva.

10

11 **LIVE-ATTENUATED CHIKUNGUNYA VIRUS VACCINE CANDIDATE**
12 **(VLA1553)**

13

14

15 **DR. BENDER:** Thank you very much for the
16 invitation to see this committee and to discuss with
17 you the best way forward for the development of a
18 chikungunya vaccine. I will divide my presentation in
19 four parts: a brief introduction to our company and the
20 candidate. Then I'll re-propose the development
21 approach moving forward, followed by some pre-clinical

1 and clinical data from our candidate and the next
2 steps.

3 Valneva company is a fully integrated
4 specialty vaccine biotech company, including R&D,
5 manufacturing, commercialization of vaccines for
6 infectious disease with unmet medical need. We have
7 currently two trial vaccine on the vaccines, a cholera
8 vaccine DUKORAL and IXIARO, which is the only licensed
9 JE-vaccine for travelers in the U.S. and EU, with more
10 than 8 million doses supplied for travelers in the U.S.
11 military. We have an adequate industrial and
12 commercial infrastructure to integrate further
13 travelers' vaccine, such as chikungunya. Our R&D
14 portfolio includes two very interesting candidates. We
15 have the only clinical stage Lyme disease vaccine
16 candidate and the chikungunya vaccine candidate we talk
17 about today. We have an international footprint with
18 about 500 employees meanwhile with locations in the EU
19 and North America for manufacturing, R&D, and sales and
20 marketing. We have a strong U.S. presence.

21 Our candidate, with a development code

1 VLA1553, is live attenuated. We develop it as a single
2 dose chikungunya vaccine for travelers and the military
3 but also for populations living in endemic countries,
4 as well as for outbreak prevention and interruption.
5 The candidate single dose attenuated lyophilized
6 vaccine; the attenuation was done with reversed
7 generics. You can call it rational design, resulting
8 in a 60 immuno-acid deletion within the known structure
9 protein three in the genome of this virus. And this
10 does not revert back even in passage 20 times on Vero
11 cells. The vaccine candidate is highly purified, Vero
12 cell culture derived drug substance manufactured in a
13 dedicate full commercial cGMP facility at FDA approved
14 site where we also manufacture Ixiaro.

15 We have Fast Track status for our program from
16 the FDA. We work together with the Coalition for
17 Epidemic Preparedness Innovations, particularly to make
18 this vaccine also available in low, middle income
19 countries. Phase one data in 120 subjects supported
20 the safety, excellent immunogenicity, and the
21 protection against vaccine induced viremia by our

1 chikungunya vaccine candidate.

2 So how would we think is the best way forward
3 for our chikungunya vaccine candidate? And there is
4 some repetition, but I find the alignment with other
5 presenters quite supportive for the discussion today.
6 So the unique epidemiological pattern of chikungunya
7 virus outbreaks makes, in our point of view, field
8 efficacy studies impossible. Neutralizing antibodies
9 offer an endpoint that is highly likely to predict
10 efficacy. The immunological correlate of protection we
11 are on the way for our candidate to establish with
12 passive transfer in non-human primates. The vaccine
13 effectiveness we would verify in phase four studies.
14 So what we propose is the licensure of our chikungunya
15 vaccine candidate by the way of accelerated approval
16 pathway using a defined neutralizing antibody titer as
17 an endpoint. Given the emerging medical need, Valneva
18 aims to make our candidate available in the U.S. by
19 2023.

20 You have seen before that the chikungunya
21 epidemiology is very dynamic. It's explosive

1 outbreaks, which are, however, short-lived. The timing
2 and the location are not predictable. Two years ago, a
3 very competent colleague said the next outbreak is in
4 Peru. I'm waiting for that. That might happen. The
5 interepidemic periods are having very limited
6 transmission, and you see on that slide two examples, a
7 larger one from Mauritius and a smaller one in Italy.
8 And they show the same pattern. More or less, in a
9 month it's over, and the precursors, early signs that
10 something's happening are not clear and not strong.

11 As we already said, in the interepidemic
12 periods the annual incidence is very variable and
13 limited, and previous speakers have related that to the
14 difficulty to have a reliable sample size. And it
15 varies hugely and recently, in the Brazil situation,
16 you have heard from Professor Mandl that you could go
17 up to subject numbers of 100,000, which is a challenge,
18 particularly when you chose the wrong region for your
19 study. The startup, these are technical
20 considerations. It takes more time. And also the
21 issue, which is sometimes here, you have a ready to go

1 steady network covering all possible sites in regions
2 and countries where the next outbreak might happen is
3 almost impossible. It's the number. They need to be
4 on standby. And even if they are ready to go, which is
5 an opportunity cost because in that period, for
6 example, they couldn't do other important studies in
7 the region. They might still miss the outbreak. And I
8 personally believe, in that situation, it would be a
9 waste of resources.

10 Neutralizing antibodies are an endpoint that
11 is highly likely to predict efficacy. The natural
12 infection is considered to give lifelong protection.
13 Animal and human data indicate that it is the
14 neutralizing antibodies that give protection. We have
15 seen repeatedly that neutralizing antibodies in passive
16 transfer studies do protect. And in other vaccines for
17 closely and distantly related arboviruses, a correlate
18 of protection was established and served its purpose,
19 for example, by yellow fever, Japanese encephalitis,
20 tick borne encephalitis and others.

21 We have seen from studies and have already

1 seen this morning that there are serological thresholds
2 which are associated with protection after natural
3 infection. You have seen more details on that
4 Philippines study, which is, however, a very good
5 example to use. For our vaccine candidate, the
6 neutralizing antibody titers are in the same range as
7 sera from naturally infected CHIK subjects and
8 conferred protection against viremia after a
9 revaccination, which is a homologous re-challenge, if
10 you wish, in its phase one study. We will have a look
11 at that in more detail a bit later.

12 So we are working obviously closely with the
13 competent regulatory agency, the FDA, to establish an
14 immunological correlative protection. We want to
15 submit the result of that ongoing study by December, so
16 very close. The protocol was reviewed, and some
17 particular questions included -- one, for example, is
18 in that passive transfer challenge study to
19 particularly check the joints of those cynomolgus
20 macaques and try to add to the scientific knowledge of
21 what's going on in infection in these very important

1 target organs and tissues. The challenge was rather
2 high for those non-human primate studies, 100 times the
3 animal infectious dose, 50. We mostly looked at the
4 virus load and the joint swelling after the wild-type
5 CHIK challenge.

6 We think that with accelerated approval
7 pathway for licensure the vaccine effectiveness could
8 well be studied post-licensure. And we would do this
9 with observational studies or others, as agreed on with
10 the Agency, in endemic areas. Arguments is by then the
11 widespread availability and use of vaccine would help
12 for those studies and a practical thing that those
13 studies could be targeted and implemented clearer and
14 more efficient and effective.

15 Now some data on our vaccine candidate, both
16 for pre-clinical and clinical. Pre-clinical we have
17 tested in our vaccine candidate in non-human primates
18 in active immunization. And the vaccine created high
19 immunogenic results and strong and long-lasting
20 neutralizing antibody levels. The vaccine candidate
21 protected against wild-type challenge in the non-human

1 primate model, no viremia observed in vaccinated
2 animals upon challenge with wild-type chikungunya
3 virus, and no anamnestic response. The clinically
4 typical manifestations of wild-type infection in Rhesus
5 macaques could be prevented with our vaccine candidate.
6 And the vaccination itself, the active vaccination
7 didn't cause any clinical manifestation. Our candidate
8 showed a delayed and strongly, by several lot scale,
9 strongly reduced viremia as compared to wild-type.

10 Now, this is the design of our phase one
11 study. In general, it is a pretty straightforward
12 design comparing a low, medium, and high dose with the
13 little specialty that, in the high dose group, we split
14 the subjects in two arms at the month six. And one arm
15 of those we revaccinated. And as I said, we called it
16 a homologous virus viral challenge.

17 The results are shown here. So on the left,
18 in the summary -- oops. We have excellent
19 immunogenicity profile after single vaccination with a
20 100 percent seroconversion rate at day 14. After a
21 single dose, 96 percent of subjects with a 16-fold rise

1 in antibody titers, high GMTs in all dose groups
2 ranging from 593 to 687, and the 100 percent
3 seroconversion rate and high GMT levels were sustained
4 until month six. We continued measuring. Upon
5 revaccination, no anamnestic response, no vaccine
6 strain viremia.

7 Safety, of course very important when you look
8 at live attenuated vaccine, and we had no related
9 serious adverse events and no adverse events of special
10 interest until month seven, which is our current
11 analyzed datapoint. Local tolerability was excellent.
12 Systemic adverse events included short-term fever,
13 headache, fatigue, and muscle pains, as expected. The
14 low and medium dose group had the superior safety
15 profile and were well-tolerated compared to the higher
16 dose group.

17 This shows the viremia on the left after
18 priming, one dose priming, the three dose levels after
19 two weeks. There was no detection possible of genome
20 equivalence in any of the subjects. On the right side,
21 you see the viremia after re-challenge, and you see

1 nothing because it could not be detected. Here is a
2 graph showing the seroconversion rates, which is pretty
3 straightforward with micro NT of 20 as benchmark and,
4 after two weeks, 100 percent seroconversion. If you
5 would use other thresholds for our RNT levels of 40 and
6 80, you still would have 100 percent seroconversion at
7 day 28.

8 Now, where do we go from here? So what we aim
9 to proceed with in a pivotal is with a correlate of
10 protection. We go -- we want to start in 2020 with a
11 classical design, age range above 18, to be conducted
12 in the U.S. The phase one study was also conducted in
13 the U.S. in CHIK naïve population with multiple sites.
14 We would look into antibody persistence and
15 neutralizing antibodies determined with a validated
16 micro PRNT. Post-licensure, as we would propose, phase
17 four effectiveness in endemic areas, co-vaccination
18 studies, particularly in some of the regions we discuss
19 is, for example, cocirculating virus like (inaudible)
20 of relevance seroprevalence of these other viruses or
21 not.

1 The pediatric development plan is under
2 development. We want to do a phase three adolescent
3 study in endemic regions and lower age groups we target
4 post-licensure. But this is to be negotiated with the
5 regulatory authority.

6 So in conclusion, we believe our live
7 attenuated chikungunya virus vaccine is safe and
8 immunogenic as shown in our phase one study. The lack
9 of viremia after homologous challenge we think as an
10 early indication of efficacy. We want to accelerate
11 the program because of the high medical need. Nobody
12 knows, and I believe after this morning's session we
13 are all on the same side here. Nobody knows when and
14 where the next outbreak happens, high medical need. I
15 would even say some urgency. And we want to use a
16 correlative protection for the further development.
17 This is ongoing in non-human primates, and we are
18 looking to discuss with you and the FDA how to proceed.
19 Thank you very much.

20 **DR. EL SAHLY:** Thank you, Dr. Bender. We will
21 be now asking questions to all four members of the

1 industry who presented data on their respective
2 vaccines. I wonder if they either can sit close to the
3 microphone over there or over here to be able to answer
4 those questions. I'll give you a minute to move.

5 So I will begin by asking, I guess, a general
6 question to all four members. Thank you for all these
7 presentations on the promising safety immunogenicity
8 data and giving us a sense of the challenges that will
9 be faced in the event of a phase three clinical trial
10 with a classical endpoint of efficacy against either
11 clinical or subclinical disease. I wonder what your
12 results would be regarding the perceived challenges
13 being a result of what we know about chikungunya
14 transmission once it's established in a region or what
15 we don't know about chikungunya transmission after its
16 establishment.

17 Meaning, a couple of studies come to mind, the
18 one from the Philippines and the one from UC Berkeley
19 where actually they were looking for dengue, but they
20 found chikungunya -- do indicate that, with reasonable
21 sample size, some attack rate can be observed. And

1 it's in line with dengue or others. And I doubt that
2 this was serendipity in two studies, but I wonder what
3 your take would be on that.

4 **DR. WARFIELD:** I don't know if this is on. I
5 guess one thing comes to mind is one of the graphs that
6 Dr. Powers showed this morning, and I believe it was
7 Colombia. Is it Colombia or Brazil where it shows
8 surveillance over a long period of time? It was maybe
9 five or ten years. And essentially, you can see in
10 that graph that the dengue incidence is very stable
11 across that time. And then there's that big blip of
12 chikungunya. There also happened to be zika that
13 happened, too, right?

14 But they were looking, and they really didn't
15 see it over that period of time. I guess in the case
16 of Nicaragua, my understanding of that outbreak is
17 really that they were looking for dengue, and they
18 found chikungunya. But within one year, by the second
19 season, it really burned itself out very quickly. So I
20 think that's the real problem is, even if you can catch
21 it, it goes away so quickly it would be very difficult

1 to set up a trial in that place and catch it in enough
2 time to catch the events that you have to get to
3 demonstrate efficacy.

4 **DR. BENDER:** We and other organizations worked
5 with potential partners in particularly Brazil and
6 India and discussed what we could do. And in those
7 discussions, I would conclude as a result what you just
8 confirmed. They are willing. They have networks,
9 particularly from dengue sites. There are structures,
10 but they are not very confident, I would say, that you
11 could just use those where chikungunya is cocirculating
12 and really catch enough incidence to show efficacy.

13 **DR. RAMSAUER:** If I may comment, I'm Katrin
14 Ramsauer from Themis. So we've looked into this quite
15 detailed in many scenarios. How could we implement the
16 trial and explain the detail? Those outbreaks were
17 really short. And a lot of these data that were
18 presented were generated after the outbreak was already
19 over. Also, the studies from Nicaragua, as far as I
20 know, this was done retrospectively when they went back
21 and looked at the samples. So this is still a big, big

1 issue.

2 A lot of the outbreaks that are reported are
3 really based on only clinical diagnosis, so there is no
4 really solid data. And then how would that fit into
5 the setup of a clinical trial? Even if we would at the
6 day one would be called, okay, there was an outbreak,
7 we would have to set up this outbreak and continue
8 surveillance. So this is very unlikely.

9 The whole epidemiology will not change if the
10 vaccine is licensed through an accelerated approval
11 pathway. The epidemiology will stay the same. It will
12 stay difficult. But then if the vaccine is already
13 approved, it will be easier to implement the vaccine,
14 implement the trial maybe, or implement the use of a
15 vaccine as soon as it's approved. The response to an
16 outbreak could potentially be faster.

17 **DR. EL SAHLY:** Dr. Gans?

18 **DR. GANS:** Thank you so much for sharing your
19 work and your ideas on how we can move forward in
20 making a vaccine for this. I had a couple of just
21 thoughts to put out there in terms of how we speak

1 about some of our correlates of protection, which are
2 heavily now being used as humoral immunity as the,
3 quote, sufficient immune correlate to protection.
4 Clearly, humoral immunity in all the scenarios that
5 you've described is really developed with an intact
6 immune system. And while we can take those antibodies
7 and transfer them, which we've shown for many, many
8 diseases, are protective against viral replication in
9 that scenario. So that's obviously a very important
10 immune correlate.

11 But we have to be very careful when we discuss
12 that in terms of something that for a vaccine that's
13 supposed to induce sort of immunity ongoing and in
14 special populations. So what has been shown, that even
15 for instant things where measles -- where we know we
16 have passive antibody. That's protective. We know we
17 can give immune globulin that is protective. The
18 vaccine is not always protective in people who are
19 deficient in other parts of their immune system.

20 And the reason why this is important is that
21 special populations, including children, may not always

1 have the same immune correlates that you have in these
2 protective environments. So I would urge the people
3 who are looking at this to actually diversify their
4 ability to look at the immune response and actually
5 look more broadly, even in these early stages, because
6 it may become very particularly important, particularly
7 in some of the areas in which you actually are
8 vaccinating. And no one has talked about co-infection
9 with HIV. So these areas do have co-infection with
10 HIV, and this has become particularly important because
11 the ways in which we develop humoral immunity and T
12 cell immunity in those deficient populations are very
13 different than what we see in the normal immune. So we
14 have to be very careful about that, and I would like
15 people to think about that as they're moving important
16 -- so HIV co-infection in children.

17 So that's one question for everybody out
18 there. And then I had some particular continued
19 concerns with the live attenuated vaccines. A couple
20 of them are why you would actually think you would need
21 two doses. So the final speaker spoke about having no

1 amnestic responses, so obviously you don't boost after
2 that second dose. So it's not really the way it works.
3 So why would you need it and why would you need two
4 doses for the first one? But the real challenge with
5 live attenuated vaccines, obviously, is in individuals,
6 particularly when you have the measles component, but
7 any live attenuated vaccine whose, again -- immune
8 systems maybe aren't adequate and we can't vaccinate so
9 again, the idea of HIV co-infection in those
10 populations.

11 The only last thing, I appreciate the last
12 speaker's inclusion of pediatrics. When we saw the epi
13 data this morning, this is an important population that
14 we have to think about. As you immunize all of your
15 adults, it's really going to shift down to being all of
16 the cases, obviously, in the pediatric population. So
17 to have at least a phase that you're thinking about
18 doing something for those individuals. Thank you.

19 **DR. EL SAHLY:** Dr. Gruber?

20 **DR. GRUBER:** Yeah. Can I just make a very
21 brief comment, clarifying comment? And that is that

1 this discussion, and I appreciate the points are being
2 made, but this discussion is really centered around the
3 feasibility of demonstrating effectiveness by way of
4 field trials. What does the animal models tell us?
5 What approach we can use to demonstrate effectiveness.
6 We should not be discussing specific products or the
7 pro or cons of a certain vaccine candidate. So this
8 should not be part of today's discussion. Thank you.

9 **DR. EL SAHLY:** I think he was first. Mr.
10 Toubman.

11 **MR. TOUBMAN:** That's okay. This is grating.
12 It's now three questions so cut me off. The first one
13 is on the question, again, of the animal studies.
14 Themis says that the symptoms of naturally acquired
15 CHIK is highly similar to humans. That's actually not
16 true because the symptom that we all care about is
17 arthritis, arthralgia. And everybody agrees you don't
18 have that in animals. So that's the thing that
19 matters.

20 My specific question on this one is for the
21 person from I believe it was Moderna, which is the

1 suggesting that you sort of a marker for it. Yeah. We
2 don't have arthritis, but we have joint inflammation.
3 And I didn't understand what that meant and how that
4 actually is going to be really reliable for arthritis
5 when that's the real problem. And these animals don't
6 have that problem. That's my first question.

7 My second question is about the post -- at
8 least two of them have suggested they would do post-
9 licensing random studies trials. Another one says that
10 infeasible because then you have the issue of doing
11 placebos on people when you already have licensure, and
12 that's problematic. And also, the arguments against
13 the feasibility seem to be the same pre or post
14 licensure anyway. So I don't understand that.

15 But the last thing, getting to the heart of
16 the question, like Dr. Gruber just said, the heart of
17 the question we've been asked is feasibility of
18 randomized controlled clinical disease endpoint
19 efficacy trials -- feasibility. And I'd like to ask
20 the question, taking money out of it, taking cost out
21 of it, I'm asking why is it not feasible? I note that

1 Moderna did say they saw it was limited feasibility,
2 not it was infeasible. It was limited feasibility;
3 whereas, of course, Themis says it's impossible.
4 Valneva says it's impossible, and Emergent says, well,
5 it could take ten years and there's considerable risk
6 of the trial being underpowered.

7 Why couldn't we -- the last part of this
8 question is why couldn't pre-licensure there be, taking
9 cost out of it -- go ahead and do the studies in
10 various places where we've seen recurrence, where you
11 see it's emergent? So you have several different
12 locations, and then you've already gotten that part of
13 it done. And then when an outbreak happens, you've
14 already addressed the immunization part, and now you're
15 going to be studying what happens. Why is that not
16 feasible, taking money out of it? Thank you.

17 **DR. RAMSAUER:** So thank you for this question.
18 That's a very good question, of course, taking money
19 out of it. Of course we would like to say it's not
20 feasible because it's expensive, but that's not the
21 reason. We can look at what's happening to Ebola right

1 now. So there was a huge outbreak. There was a lot of
2 activity getting a vaccine into the field as quickly as
3 possible. There were clinical trials done under so
4 called public health emergency that allowed a much
5 faster turnaround of clinical trial applications.

6 There were several clinical trials. And even under
7 this special circumstance, with this focus in a disease
8 on development of vaccines, it was impossible to start
9 a vaccine trial in time to hit the huge Ebola outbreak.

10 And now, chikungunya is a huge disease. There
11 is an urgent medical need. We all agree that it's good
12 to have a vaccine. But even under this huge explosive
13 outbreak in Latin America, it wasn't a public health
14 emergency. So all the special tools that allow fast
15 implication of a clinical trial were not there. So
16 this would depend on the willingness of local
17 regulators in affected countries to get clinical trials
18 started up quickly. And this hasn't happened. I'm not
19 blaming any country. It just didn't happen.

20 And again, if we get information on starting a
21 clinical trial the first day, even if the protocol is

1 ready, there is things like import permits that are
2 required. Sites have to be set up. We've seen
3 chikungunya outbreaks are very focal. What if I have a
4 great hospital setup in one area but the outbreak is
5 actually happening 1,000 miles away? It's impossible
6 to recruit those people into that hospital I have set
7 up and many other factors that doesn't have anything to
8 do with money. That's really logistics and the
9 availability of data for the outbreak. That's why it's
10 not feasible.

11 **DR. EL SAHLY:** We're going to take one last
12 question because we're going to break at 1:00.

13 **MR. TOUBMAN:** I had two other questions.

14 **DR. EL SAHLY:** There are many questions,
15 actually, not just one. We're going to take one of
16 them and then break at 1:00, reconvene because the open
17 public hearing statement time cannot be changed, and
18 then all the questions will be asked. So Dr. Bollinger
19 and then we'll break.

20 **DR. BOLLINGER:** Thank you. I just had a
21 question for all of the sponsors. So I think it's

1 evident that there is an unmet medical need. I haven't
2 seen any evidence that says that there's an unmet
3 medical need only for patients older than 18. So in a
4 world where the virus doesn't discriminate by age, I'm
5 wondering do you have evidence why you would initiate
6 pediatric data gathering now? And if you don't have a
7 scientific rationale, would you consider going into
8 pediatric patients earlier, so we don't leave them
9 untreated or unvaccinated?

10 **DR. WARFIELD:** Kelly Warfield from Emergent.
11 We're currently planning and are having active
12 discussions around our phase three clinical study and
13 are contemplating enrolling adolescents into our phase
14 three. And then we have a pediatric plan in front of
15 EMA and will be having those discussions post our end
16 of phase two meeting with the FDA. But I think we see
17 no reasons why we could not initiate pediatric studies
18 fairly soon. Our safety profile seems to support that
19 to date, clearly.

20 **DR. BENDER:** I guess everybody would say the
21 same, so thank you.

1 **DR. EL SAHLY:** Okay. Break time. We will
2 have a 40-minute lunch break, right? Am I right? 40-
3 minute lunch break, reconvene, and ask more questions.
4 Thank you.

5

6 **[BREAK FOR LUNCH]**

7

8

9

OPEN PUBLIC HEARING

10

11 **DR. EL SAHLY:** Good afternoon, everyone. I
12 would like to invite everyone to take back their seats
13 so we can get started. This will be the Open Public
14 Hearing session of the meeting today. We have no one
15 registered on the phone to give a public statement. I
16 wonder -- and I actually invite anyone in the room, if
17 they have a public statement. Anyone attending in the
18 public in the room?

19 Okay. No one is stepping up to the microphone
20 and no one is registered online, so this concludes the
21 Open Public Hearing session. We had a few questions to

1 the manufacturers. I had a couple of my colleagues
2 with their hands raised before break. We will begin
3 with Dr. Michael Kurilla.

4

5

DISCUSSION

6

7 **DR. KURILLA:** Yeah, so, it looked like there
8 had been quite a bit of data generated regarding the
9 passive transfer in the non-human primates. It seems
10 that in all the instances I saw, that's always been of
11 a serum coming from vaccinated individuals. I'm
12 wondering, has there been any attempt to utilize
13 convalescent serum from people who have sustained a
14 chikungunya infection, and use that as a way to further
15 refine the protected dose? And in addition, have you
16 been able to discern any qualitative or quantitative
17 differences between the vaccinated serum and
18 convalescence serum?

19 **DR. RAMSAUER:** We have done it as we've shown
20 the data for animals that received serum pooled from
21 vaccinated subjects. But we also had a group of

1 animals that received serum from chikungunya patients
2 with the same result. Yes, it's also a way to define a
3 correlative protection with convalescent. But in the
4 end, we want to show that the vaccine is working.

5 So, the correlate would come with serum from
6 vaccinated subjects, but also studies for their
7 qualitative humoral response between -- as the humoral
8 and cellular responses, we have studies ongoing to
9 compare previously infected subjects and vaccinated
10 subjects. So, that's coming.

11 **DR. ATREYA:** If you could please speak into
12 the microphone that would be helpful; because people
13 are not able to hear you well.

14 **DR. RAMSAUER:** Thank you.

15 **DR. EL SAHLY:** Okay. We had -- I think Dr.
16 Meissner had a question.

17 **DR. MEISSNER:** Thank you. I wanted to thank
18 all the presenters this morning. It was, I thought,
19 quite an exciting overview of next generation vaccines
20 and where the field of vaccinology is going. I found
21 it very informative.

1 Secondly, it's always -- I understand the
2 issue of cost. And I agree with Mr. Toubman. You can
3 take that out of the equation, but of course you really
4 can't take it out of the equation. And if you folks
5 aren't making next generation vaccines, then we can't
6 make recommendations to use them.

7 It's a very difficult situation. I think it's
8 a problem that we're all confronting. There has to be
9 a sufficient incentive to develop new vaccines and to
10 bring them to market. We also realize that it's an
11 enormously expensive undertaking. And for vaccines
12 that will have limited use, it's even more difficult
13 because the cost of developing that vaccine will pretty
14 much be the same to complete the clinical trials and go
15 through the regulatory process.

16 I think this is going to be an increasingly
17 important issue in the future. But I guess my
18 sentiment is that whenever we start to skip a step on
19 approval, that it sometimes comes back to haunt us.
20 And I think the absence of an efficacy trial -- I worry
21 that that's a slippery slope, that it's a dangerous

1 precedent to establish. We have done that for other
2 vaccines, obviously, with the latest generation
3 Prevnar, and meningococcal vaccines we use a serologic
4 correlate rather than an efficacy. But this is a
5 little bit different because there isn't an existing
6 vaccine.

7 For example, how about, it's not only efficacy
8 but also safety. How about when you begin to vaccinate
9 large numbers of people who are seropositive? How
10 confident are you that there won't be some
11 unanticipated adverse event?

12 I guess it's not so much a question as it is
13 kind of a comment in regard to I don't think we have a
14 good animal model, I don't think we have a convincing
15 surrogate; and I just worry about unknowns if we don't
16 do an efficacy trial. Because you won't be able to do
17 it in post-licensure. You won't be able to get the
18 same data in a post-licensure Phase IV study.

19 Thank you. That's all that I wanted to say.
20 I don't know if anyone wants to comment.

21 **DR. EL SAHLY:** Dr. Gruber wants to comment.

1 **DR. GRUBER:** I just wanted to clarify
2 something, and that's regarding the comment, Cody, you
3 made regarding safety. Even if we assume that an
4 accelerated approval is going to be the path forward,
5 there is still a requirement for pre-licensure safety
6 studies, even under that approval pathway. Okay? Just
7 thought I'd make this comment.

8 **DR. MEISSNER:** And so, what does that mean
9 then in terms of data?

10 **DR. GRUBER:** Well, we would have to sit and
11 discuss with the individual vaccine manufacturers the
12 size of the pre-licensure safety database that we think
13 is necessary to support the safety of the product. And
14 of course, it will depend on the vaccine candidate and
15 what the data from Phase I and II clinical studies look
16 like, the safety data. But there would be pre-
17 licensure safety studies.

18 **DR. MEISSNER:** And that could be a smaller
19 population than ones that demonstrate efficacy. Is
20 that what you're saying?

21 **DR. GRUBER:** Not necessarily.

1 **DR. MEISSNER:** Okay.

2 **DR. EL SAHLY:** Dr. Janes?

3 **DR. JANES:** Thank you. Thanks for the
4 presentations and helping us all to understand the
5 sources of data and the potential pathways. I had two
6 questions. One is probing further on the data that
7 exists in humans to speak to whether or not the
8 neutralizing antibody titer is an adequate surrogate
9 for basing licensure decisions on. I recall a couple
10 of studies that were shown demonstrating that the risk
11 of infection was considerably lower, I think even zero
12 in one study, among individuals who had a positive
13 antibody response as compared to individuals who did
14 not.

15 It seems to me that it's particularly
16 challenging to validate a surrogate in this context,
17 given that the hypothesis is that prior infection
18 essentially prevents a person from becoming
19 subsequently infected. If that's true, I wonder the
20 extent to which the association that's been observed
21 between the neutralizing antibody titer and infection

1 risk is really just marking the fact that prior
2 exposure is a predictor of subsequent infection, or
3 those with an antibody response presumably. Those are
4 those who were previously infected.

5 To what extent has the neutralizing antibody
6 titer itself been kind of isolated as the sole or
7 strongest predictor of infection risk, as opposed to
8 the other types of immune responses that might be
9 mounted following infection?

10 **DR. MANDL:** This is a very important question.
11 And the best answer that instrumentally can be given is
12 by a passive transfer study. Because there, at least
13 we know that all we transfer is antibody. And we look
14 for its effect, which would be protection.

15 Does that totally exclude that after natural
16 infections other factors may be involved? No. But
17 does it show that antibody by itself is sufficient to
18 provide protection? I would argue, yes; with the
19 limitation, of course, that it's done in an animal
20 model.

21 And perhaps I can take this opportunity to

1 also kind of comment on your comment before we had the
2 break, about the animal model, perhaps just to clarify
3 that I didn't want to say that the clinical
4 presentation is exactly the same, although very similar
5 between non-human primates and humans. But the course
6 of infection, if we choose a route like intradermal
7 inoculation and an infectious dose that is similar to a
8 mosquito bite is highly similar, including the invasion
9 of joints by the virus.

10 What's missing is the ability to measure the
11 pain, as a source of the arthralgia. It may be
12 possible to measure some inflammation parameters. I
13 think in Scott's talk following this discussion, we
14 will hear more about this. But I just wanted to
15 clarify that in light of all this, we still believe
16 that the non-human primate model is as good as an
17 animal model can ever get.

18 And to your question, I think passive transfer
19 is really better than an active immunization in that
20 case. Because there you could still argue if you
21 immunize with this or that kind of a vaccine, it may be

1 different from an infection; but here you really
2 transfer the antibody and you look exactly what is the
3 effect of the transferred antibody. I think from a
4 scientific point of view, that's as good as we can do
5 it.

6 **DR. JANES:** My second question is around the
7 post-licensure study designs to validate really the
8 efficacy and effectiveness of a candidate vaccine. I
9 wonder if any of the developers are willing to comment
10 on what specifically they envisioned for study designs
11 in a post-licensure period, and how exactly those
12 designs would be more feasible to implement than the
13 pre-licensure efficacy trials?

14 I heard mention of kind of a pre/post
15 contrast, comparing incidence of disease prior to the
16 rollout of a vaccine as opposed to after the rollout of
17 a vaccine. But of course, that design would be
18 enormously compounded by any temporal trends in
19 incidence within the population. I wonder if you can
20 comment on how you envision validating the clinical
21 efficacy.

1 **DR. EL SAHLY:** Any other questions? Any
2 comment? They have a comment? Okay.

3 **DR. DE LAME:** Hello there. I'm vice president
4 of clinical development for Emergent.

5 **DR. EL SAHLY:** We can't hear you.

6 **DR. DE LAME:** Let me do something. Is this
7 better this way?

8 **DR. EL SAHLY:** Uh-huh.

9 **DR. DE LAME:** Now I speak like Mike Trager.
10 Paul-Andre De Lame, Vice President of Clinical
11 Development at Emergent. We have been thinking about a
12 number of possibilities in terms of designs. One would
13 be, as was alluded to, start looking for the current
14 state compared to the future state after a significant
15 campaign of vaccination is in a selected area. That's
16 one way to go.

17 A big advantage of waiting for approval on an
18 accelerated pathway is that it does make access to
19 vaccine much easier. And that opens up a number of
20 things including the time window; where you could
21 actually comment that many have been made. You can

1 take it away or not take it away. Time, you cannot
2 take away.

3 And the predictability of the episodes of
4 chikungunya disease is, as we saw, not new. So, if
5 time can be taken somewhat away by having a vaccine
6 available, then you can start vaccinating even with
7 possibly a randomized control trial, if you want to,
8 and think that it is ethical. You can vaccinate a
9 preparation and wait. And if you have to wait forever,
10 it doesn't matter. You can wait. Except that, with
11 time of course, cost accumulates.

12 There are many possible options that open
13 after approval that are not realistic before approval.
14 I hope that this helps.

15 **DR. JANES:** So, do we understand you to mean
16 that basically the supply of the vaccine would be such
17 that you could envision rolling it out and implementing
18 it in a very large population where it's --

19 **DR. DE LAME:** I'm just saying those are
20 possibilities that remain totally theoretical at this
21 point. But just to explain that there will be many

1 more choices than what would be available today. And
2 it would be much more feasible.

3 **DR. EL SAHLY:** Dr. Bollinger.

4 **DR. RAMSAUER:** Okay. I can also comment to
5 this, so I had time to think about it. Now I lost
6 track. Oh, God. No, so, it was what Christian said
7 during his talk is that -- so, what we call post-
8 licensure at first is really not post-licensure, that's
9 something that's already ongoing. But obviously, we
10 don't start a post-licensure effectiveness study
11 already, but we, of course, started thinking about it.
12 And one of the things we do is -- please correct me. I
13 don't know how many countries were affected of
14 chikungunya, but I think it's over 100. And we cannot
15 possibly set up 100 countries to start a clinical
16 trial.

17 But what can we do is think about what could
18 be a country that could have chikungunya transmission?
19 I mean, there are several countries in Southeast Asia
20 and in Latin America that are -- there's Brazil,
21 Thailand, obviously, something like this. And then

1 what countries do also provide an infrastructure that
2 allow large trials? And it's not all the countries in
3 the world do that, but particularly Thailand and Brazil
4 were involved in large clinical trials as we've seen
5 for dengue. So, those would also be countries where we
6 would put a focus on.

7 Then, there are other aspects that could go
8 into it. There are countries that have vaccine
9 registries where you could, for example, start a larger
10 vaccination campaign with an approved vaccine. And if
11 these countries have vaccine registries, you could
12 collect data on do people who report with chikungunya
13 or chikungunya-like symptoms, were they vaccinated
14 before? So, this would be a strategy; we have started
15 working on this really. Try to select specifically
16 countries where this could work for those reasons.

17 **DR. EL SAHLY:** Dr. Bollinger?

18 **DR. BOLLINGER:** Thank you. So, thinking about
19 the four vaccines that we heard about today kind of
20 being in concurrent development. I'm thinking that
21 that obviously has a public health benefit because you

1 can meet the needs of patients with different
2 characteristics as well as ensuring that there is a
3 continuous supply of vaccines should one manufacturer
4 have a difficult time with their vaccine.

5 I'm wondering -- we've heard about all of the
6 difficulties with feasibility; have your assessments on
7 feasibility been done purely looking at developing your
8 product? Or have you also thought about the impact of
9 having other vaccines competing for that small patient
10 population? Is it even less feasible than what you
11 think to do a randomized controlled study, because
12 you're going to be competing for patients with other
13 companies?

14 **DR. WARFIELD:** Kelly Warfield, Emergent. I
15 mean, I think as far as we're concerned, we really
16 haven't thought about the fact that there's multiple
17 developers at the same time. I mean, it's really just
18 based on the data and the feasibility of actually
19 performing the trials. I think if it was feasible for
20 one of us to do it, it would be for any of us to do it,
21 one vaccine, multiple vaccines. I mean, it's really

1 just a logistical challenge. And it's a real challenge
2 of not being able to predict where the outbreak is
3 going to occur or to actually be able to do a trial in
4 an endemic region.

5 As we saw this morning, there's just a few
6 hundred cases potentially in some of these places. You
7 would have to potentially vaccinate millions of people
8 and then really wait long periods of time to hope that
9 there was enough of an attack rate in a large enough
10 number to be able to show vaccine efficacy. I really
11 just honestly don't believe it matters that there's
12 multiple of us here.

13 **DR. EL SAHLY:** Dr. Fischer?

14 **DR. FISCHER:** Two questions. One is a follow-
15 up to Dr. Janes' question, and maybe it was answered in
16 the last response. But for a post-licensure study, are
17 you proposing that there would be still a clinical
18 endpoint? Or would you propose that there would be an
19 immunologic endpoint that was established as the basis
20 for licensure?

21 The second question is about neutralizing

1 antibodies, which, I think, are promising as an
2 immunologic surrogate, at least of protection, for
3 various reasons. But all off the manufacturers
4 presented their data using different assays and
5 different cutoffs; so I'm wondering how, essentially,
6 would the commitment be made, or the decision be made
7 to what the actual immunologic correlate would be that
8 would then be met by any products that would be
9 submitted for licensure?

10 **DR. WARFIELD:** Kelly Warfield, Emergent. I'm
11 going to try to remember your questions. I think your
12 first question was around the endpoints in a post-
13 licensure study. And I really think the purpose of
14 doing a post-licensure efficacy study would be to look
15 at a clinical outcome. I mean, that's really the
16 purpose of it.

17 Clearly a case definition would need to be
18 established, whether it was just fever with a
19 laboratory-confirmed test, or if it's fever and
20 arthralgia. Obviously, the more things we add, the
21 larger the sample size needs to be because the more

1 complicated that clinical definition becomes. I think
2 if a post-licensure trial is required, then that is
3 going to have to be a clinical outcome.

4 As far as the assays, I think it's a very
5 perceptive point that you picked up. And I think you
6 saw that in many of the presentations from both the
7 manufacturers as well as some of the people that
8 presented. And if you look through the literature,
9 there's definitely different assays that are being
10 used. They're all neutralizing assays, whether they're
11 being done with an attenuated virus, like the 18125-
12 vaccine strain that was used, or a BSL-3 vaccine that's
13 being used. People are using a plaque reduction
14 neutralization 50 endpoint versus an 80 or a 90
15 endpoint.

16 Emergent, specifically, is using a luciferase
17 assay. And we've done our own comparisons and showed
18 that there's fairly a good correlation and low bias
19 between our assay and the PRNT. But I think, it's my
20 understanding -- and I'm not speaking on behalf of the
21 agency. But if every manufacturer has a negotiation

1 with the agency around what their particular threshold
2 is and what their assay is, then those two things are
3 going to be linked with all of their studies, as well
4 as the assay that they're using and not necessarily
5 with the data, per se, across the whole field.

6 **DR. FISCHER:** Can I just ask you -- sorry -- a
7 follow-up question then? Can you just explain a little
8 bit more about the luciferase assay because I'm not
9 familiar with it? Is it a plaque reduction
10 neutralization test, a microneutralization test, a
11 different test?

12 **DR. WARFIELD:** Right. So, what we've done is
13 we've taken the 18125-vaccine strain; we're able to do
14 the assay in a BSL-2 environment. And we've inserted a
15 luciferase gene into that. We use vero cells like
16 almost everybody does in the field, to perform that
17 test. And then you do dilutions of the serum to be
18 able to determine the endpoint.

19 I mean, as I said, we're using an 80 percent
20 endpoint. But the readout that we're looking for is
21 the level of luciferase that's generated within those

1 cells. But as I said, it does correlate with the
2 regular plaque reduction and we've tested that.

3 **DR. RAMSAUER:** Just to comment to the
4 comparability of the assays, there is an effort ongoing
5 from the UK NIBSC to generate an international
6 standard. So, they generated a serum pool of
7 convalescent sera and sent it out to test labs and
8 manufacturers to standardize the assays. And we are
9 participating in this effort to standardize our assay
10 also against the international standards.

11 **MR. TOUBMAN:** To follow up on my questions
12 before the break, one of which wasn't answered, and
13 also follow up now. Are any of the companies willing
14 to do post-licensure? You say you'd be looking at
15 clinical outcomes, but actually a randomized controlled
16 trial notwithstanding the difficulties. Oh, sorry.

17 Are any of the companies willing to commit to
18 doing randomized controlled trials after licensure?
19 Because you said there's ways of doing it that makes it
20 a little -- there's some, you know, comments it'll be
21 easier to do a post-licensure; even though there's

1 still feasibility issues, but it's easier. Are any of
2 the companies willing to commit to actually doing that
3 afterwards?

4 And then the second question, really for all
5 the companies -- it's really the ultimate question.
6 And that is, assuming Dr. Meissner's view is followed,
7 let's just say the FDA follows that view and says, no,
8 we can't skip that step. Before licensure, we have to
9 do randomized controlled trials. We just have to. Are
10 the companies going to drop this whole effort or not?
11 I mean, I think that's really the ultimate question
12 now. And I think we'd want to know the answer to that.

13 **DR. AUGUST:** Allison August from Moderna. I
14 can say that if a randomized controlled trial is
15 required, that that would make it untenable for Moderna
16 to go forward with this program.

17 **MR. TOUBMAN:** I'm sorry. Before or after?

18 **DR. AUGUST:** Pre. Yeah.

19 **MR. TOUBMAN:** Pre-licensure. And what about
20 after licensure?

21 **DR. AUGUST:** I can't comment on that right

1 now.

2 **MR. VYAS:** This is Manish Vyas, Vice President
3 of Regulatory Affairs for Emergent Biosolutions. So,
4 to that point, I think pre-licensure or post-licensure,
5 same challenges will remain. So, as we look at the
6 different -- how the disease progression happens
7 between different regions and countries, so
8 unpredictably will remain.

9 So, I think, to be pretty clear, I think the
10 feasibility of a randomized controlled trial, even in a
11 post or pooled scenario will be a challenge. So, it
12 would most likely be more like an observational trial.
13 Because, that way, you can vaccinate a population, be
14 able to monitor kind of a clinical outcome, but it may
15 not be a randomized control trial. So, I just wanted
16 to clarify that point.

17 **DR. DE LAME:** Paul-Andre De Lame, the Vice
18 President of Clinical Development, Emergent. I didn't
19 say that we would commit to a randomized controlled
20 trial. I said, time not being an issue, you could
21 always start it. It doesn't mean that you will ever

1 see the results.

2 So, let's assume, as Manish just said, that we
3 were to start a randomized controlled trial and it
4 never ends. Is it going to give us an answer?
5 Obviously not. So, we need to look at the best
6 alternative and the best design in the situation in
7 time, and this needs to be negotiated with the agencies
8 in the context of regulatory pathways. Make sense?

9 **DR. EL SAHLY:** Okay. Thank you all for this -
10 -

11 **MR. TOUBMAN:** There's one more company we
12 haven't heard from.

13 **DR. EL SAHLY:** Oh, one more company.

14 **MR. TOUBMAN:** Yeah.

15 **DR. EL SAHLY:** Sorry.

16 **MR. TOUBMAN:** Thanks.

17 **DR. RAMSAUER:** So, in one of my previous
18 comments, I said that the epidemiology doesn't change
19 after licensure, of course. But I did not want to say
20 that after licensure we can't do a randomized
21 controlled trial the same -- as we just heard the same

1 problems stay with this. And then, also, doing a
2 randomized or a controlled trial after licensure, what
3 do we do in an outbreak? We cannot use a placebo
4 control that's unethically viable.

5 There will be other ways of controlling this
6 trial as necessary. Maybe vaccinating one area,
7 looking at another area that was not vaccinated. But
8 then it's, again, sort of placebo controlled in a
9 placebo -- or a randomized trial. So, I think we say
10 we cannot do a randomized controlled trial before
11 licensure and the same will occur after licensure.
12 This is not possible.

13 **DR. EL SAHLY:** Yes, Dr. Kurilla?

14 **DR. KURILLA:** I think a lot of the earlier
15 discussion has really honed in on the fact that the
16 joint-related sequelae of this disease is one of the
17 major drivers. And in the absence of persistent
18 infection, which I don't think there's any evidence
19 that this is a persistent infection, one can envision
20 where viral infection causes damage to the joint, and
21 that initiates the process that goes on. The

1 alternative would be just a purely type of autoimmune
2 response that initiates the sequelae to cause the
3 ongoing inflammation and joint pathology.

4 The concern that the animal models don't
5 necessarily replicate that could be for a lot of -- you
6 know, that we see in humans could be for a lot of
7 issues. But in the absence -- so we do have clear
8 evidence there is some potential viral infection in the
9 joint space.

10 But my question is, do the manufacturers feel
11 that there has been -- so far, in terms of what's been
12 done in clinical studies -- a sufficient number that
13 would suggest that the vaccination itself is not going
14 to induce an autoimmune response that would give you a
15 sequelae on par with what we see with natural
16 infection?

17 **DR. RAMSAUER:** So we have, as we've shown,
18 done a couple of clinical trials. We have about 500
19 subjects vaccinated. We have really carefully looked
20 for any symptoms in the joints. We have defined them
21 as adverse events of special interest and carefully

1 assessed every -- I mean there are -- and reported it.
2 So, people report joint pain even if they're vaccinated
3 or not.

4 So, we carefully assessed every single report
5 of arthralgia. Could it be related to the vaccine, is
6 there any other etiology? And so far, we couldn't find
7 any link between vaccinating and arthralgia.

8 We have just completed and are currently
9 analyzing this clinical trial in Puerto Rico where we
10 had -- the population had experienced the chikungunya
11 disease probably two or three years before the vaccine
12 trial.

13 We had a couple of patients -- well,
14 previously exposed people -- in this trial who had
15 reported joint pain. We graded them with arthralgia
16 and looked really very carefully. And in our
17 vaccinated group, we found one subject; and also in the
18 control group who received MMR, we found one subject.
19 So, there is no correlation between the chikungunya
20 vaccine we have used in 500 subjects and also in the
21 pre-exposed subjects.

1 **DR. WARFIELD:** Maybe just to provide a little
2 bit of color around your comment; I think it's really
3 unclear in the field as to the cause of the arthritis
4 that happens in the chronic phase. I mean, I think
5 there's -- we looked, and maybe there's one or two
6 instances where people have taken synovial fluid and
7 looked for a virus. And there is evidence of viral RNA
8 in a couple of those biopsies of people that have
9 chronic disease.

10 I think animal studies have supported that
11 finding, the thought that viral RNA and persistence,
12 nobody can detect replicating virus in kind of those
13 long-lived studies. But certainly, there seems to be a
14 pattern that viral RNA that resides within the joints
15 is what is likely driving that. It's not what's
16 proven, I think. But I think that's where the field
17 believes that the cause is; and it's not necessarily
18 that a vaccination would necessarily cause the same
19 thing.

20 **DR. EL SAHLY:** I don't think, though, that the
21 individuals who had chikungunya and did not have

1 chronic joint symptoms were biopsied. So, I don't know
2 if this RNA -- yeah, it was uncontrolled when I read
3 it, unless new data came.

4 Anyway, thank you all for this very engaging
5 discussion. I would like to welcome now, Dr. Scott
6 Weaver. Dr. Scott Weaver is the Chair of the
7 Department of Microbiology and Immunology at the
8 University of Texas Medical Branch in Galveston. Dr.
9 Weaver will be discussing passive transfer studies to
10 determine correlates of protective immunity against
11 chikungunya fever.

12

13 **PASSIVE TRANSFER STUDIES TO DETERMINE CORRELATES OF**
14 **PROTECTIVE IMMUNITY AGAINST CHIKUNGUNYA FEVER**

15

16 **DR. WEAVER:** Well, good afternoon, everyone.
17 Thanks for the opportunity to participate. Sorry I
18 couldn't be here in the morning. But I was asked to
19 talk about passive transfer studies for you this
20 afternoon. So, what I'm going to do is just review
21 some examples from the literature. This is not an

1 exhaustive presentation with everything that's been
2 done.

3 But I'm going to provide examples from several
4 different donor species, including humans, non-human
5 primates, and mice, as well as recipient species. I'll
6 show you some of the typical results that have been
7 observed. Then, at the end, I'll pose a few comments
8 for discussion, some of which have already come up just
9 in the past half hour here.

10 So, let me begin just with a brief outline of
11 the presentation. I'm going to organize it basically
12 by donor and recipient species. And then, as I
13 mentioned, some of the limitations of these studies,
14 I'll mention at the end and some questions for
15 discussion.

16 So I just wanted to start off with one example
17 of studies showing that antibody production by B cells
18 is very important for protection against chikungunya,
19 like other alpha viruses and many other viruses. This
20 is one study done with mice that are deficient in B
21 cell production, probably nearly completely. But a

1 couple of studies suggest that this mutation doesn't
2 completely eliminate the B cell response. But it
3 certainly knocks it down quite a bit.

4 And what you can see here on the left is that,
5 without antibodies, there's a prolonged period of
6 viremia in these particular mice, black 6 mice, whereas
7 normal mice clear the viremia typically within a week
8 of infection. And then a similar finding for, on the
9 right, the joint swelling when these animals are
10 inoculated.

11 Typically, these studies in mice are done with
12 footpad inoculation and measurement of the height of
13 the footpad or the ankle joint. So, antibodies are
14 important for reducing the latter half of that footpad
15 swelling reaction you can see starting on about Day 7.
16 A lot of the mouse studies I'm going to show you
17 examples from, come from work that we did with a
18 vaccine we developed at UTMB, along with partners at
19 the Envergent company that later became part of Takeda,
20 as well as Ann Powers and others from the CDC who are
21 involved.

1 So, this is a live attenuated chikungunya
2 vaccine. It's attenuated by taking the wildtype
3 genome, which has a sub-genomic RNA, and mutating the
4 promoter for making that sub-genomic message so it no
5 longer can be made at all. And then, inserting in its
6 place an internal ribosome entry site, so the
7 structural proteins can be translated from the genomic
8 RNA. But this leads to a major down regulation in the
9 structural proteins, and a very predictable and very
10 stable attenuation in this vaccine.

11 We did a lot of studies, including some
12 passive transfer studies using this vaccine. I'm going
13 to show you a few examples here. So, first, looking at
14 the antibody response to this vaccine, you can see
15 that, when the isotypes were broken out, that the
16 dominate immune responses in IGG2A response shown in
17 red here on the left, but also other responses. And
18 when you look down here at the bottom, these are
19 neutralizing antibody titers. These are measured with
20 a plaque reduction assay and a 50 percent endpoint.
21 And you can see that the titers average about 10 to the

1 3 here, which is a very robust immune response in these
2 animals.

3 So, if you look on the right side here, you
4 can see the results from some of the passive transfer
5 studies where pooled serum from these mice -- and this
6 was done with interferon alpha receptor knock-out mice.
7 These IFNAR mice are used in the majority of the mouse
8 studies in the literature, because it's a lethal model.
9 It makes it much easier to determine efficacy when you
10 have a lethal model, and also a lot of replication in
11 the muscles and joints, and weight loss and footpad
12 swelling. So, this study was done by taking pooled
13 serum and then doing serial dilutions, shown here on
14 the right, starting with undiluted and going down to 1
15 to 40, as well as controlled normal mouse serum.

16 And then, looking at survival here in this
17 graph, and you can see that there's basically a
18 titration of the survival efficacy with titration of
19 the serum delivered to the animals. If you look on
20 Panel B here, you'll see weight change. And once
21 again, with the undiluted or 1 to 5 dilutions, you see

1 no significant change in weight of these animals, which
2 are usually about 6 to 8 weeks old at the time of
3 challenge. With higher dilutions, then you see a loss
4 of that efficacy and the mouse start losing some
5 weight.

6 Looking at footpad swelling here, again, you
7 see that with the undiluted and 1 to 5 diluted serum,
8 you see no evidence of footpad swelling. And then,
9 with the lower concentrations of the neutralizing
10 antibodies, you see more and more of this typically
11 biphasic swelling in these animals.

12 And then, after challenge, you can also look
13 for viremia. And again, the two highest deliveries of
14 the serum completely prevent viremia. In this case,
15 normal mouse serum is the only other treatment group
16 here, which it has no effect on viremia. Notice here
17 also that the serum of the mice post transfer was also
18 assayed using the neutralization test.

19 So, this is one of the studies where we do
20 have an accurate assessment of the antibodies present
21 during the challenge here. These are 50 percent

1 endpoints, so the undiluted serum produced a titer of
2 106, which is lower than typically seen, I think, with
3 vaccine trials directly, with most of the vaccines
4 we're discussing today. But if we took that out to an
5 80 percent endpoint, which is often used in the
6 literature, we'd still see probably a 20 or 40 level
7 titrating them on down to undetectable at an 80 percent
8 assay.

9 The next study was done to actually look at
10 the role of T cells. I just want to present this to
11 show you an example of what's known about the effect of
12 cellular immunity on protection against chikungunya,
13 and this applies to other viruses in the alphavirus
14 group as well. In the first experiment shown on the
15 upper two panels, the mice were depleted of CD4 and/or
16 CD8 cells with antibody treatment. And you can see,
17 looking at survival here, that these animals after
18 vaccination and after depletion show no change in
19 survival here.

20 They're still completely protected despite the
21 absence of those cells, whereas the control animals in

1 this -- again, this is the IFNAR mice. They die within
2 a week of challenge. Same thing for weight here -- a
3 depletion of T cells makes no difference for stability
4 of weight. And then, looking at the bottom here, these
5 animals had cells transferred into naïve animals, and
6 then challenge here. And what you can see is the
7 mirror image of what we find up here.

8 The transfer of cells has no impact on
9 survival. All the mice die after challenge. They all
10 lose weight very quickly before dying. If we look at
11 the footpad swelling here, they're all swelling very
12 rapidly before they die. And then there's no
13 protection from viremia by transferring in those T
14 cells. So, this is in keeping with many decades of
15 research on alphaviruses. As far as we know, cellular
16 immunity has very little, if any, impact on protection.

17 This is just another study with a very closely
18 related alphavirus called o'nyong'nyong virus, which I
19 think is relevant if we consider the need to protect
20 against all strains of chikungunya. So, o'nyong'nyong
21 is much more distantly related antigenically to any

1 strain of chikungunya than the inter-chikungunya
2 diversity that we see in nature. But this particular
3 vaccine when we transfer serum -- again, into the
4 IFNARD model -- completely protects against fatality
5 against o'nyong'nyong virus challenge. This is done
6 with mice that have defects in both the alpha, beta,
7 and gamma interferon receptors.

8 So, this is a study done with the measles
9 virus-vectored vaccine, very similar to what I've just
10 shown you involving mice. So, after a vaccination, I
11 believe these animals received two doses. Serum was
12 transferred, again, into the IFNAR model here. Here
13 are the volumes of sera, and then the challenge dose
14 here of 10 to the 5 TCID50 into the animals. I'm
15 sorry. That's the vaccination dose. And then
16 challenged with 100 plaque-forming units of
17 chikungunya.

18 This study looked at mortality in this lethal
19 model, and you can see that animals that received the
20 measles virus vector chikungunya vaccine had almost
21 complete survival here. Animals that received measles

1 virus vaccine strain only all died as negative
2 controls. And then a hyperimmune mouse acidic fluid
3 was used as a positive control, and all those animals
4 survived. So, this is what's been published for the
5 measles system. I understand you heard more
6 information about that vaccine this morning.

7 This is an example that I wanted to present
8 because it's a different kind of vaccine. It's a
9 vaccinia vector chikungunya vaccine, but also because
10 it includes some information about the kinds of
11 antibodies -- specifically neutralizing antibodies --
12 and their effect on protection. Because vaccinia-
13 vectored vaccines generally generate a very robust
14 cellular immune response, but a more limited humoral
15 response. So, this study was, again, done with the
16 IFNAR receptor knock-out model here. But it was done
17 with vaccination of both immunocompetent BALB/c mice as
18 well as the IFNAR mice. And then protection studies
19 were done, and passive transfer studies were also done.

20 So, in this case, you can see that, for six
21 mice that here were BALB/c vaccinated mice, there was a

1 very limited neutralizing antibody response. Only five
2 of six animals had detectable neutralizing activity.
3 And those five that did have activity, even at the 50
4 percent endpoint here, very low titers of only 10. So,
5 this is generally much lower than we expect to see with
6 an efficacious vaccine. Then, when the transfer was
7 done and these animals were evaluated afterwards for
8 viremia, you can see that there was no effect of the
9 passive transfer.

10 Animals that received all of the vaccines
11 except the positive control which, in this case, is
12 that live attenuated vaccine that I just showed you
13 that we developed with these same investigators. That
14 positive control protected against viremia, but the
15 transferred antiserum from the vaccinia-vaccinated
16 animals did not. And it also did not protect against a
17 lethal outcome in this model.

18 What may be a little bit surprising but is --
19 for people working on alphaviruses for a long time,
20 perhaps not -- is that, despite this lack of the
21 ability to transfer protection in the serum of these

1 animals, they are protected by the vaccine itself. So,
2 these are just examples of studies simply vaccinating
3 animals then challenging them, the same IFNAR lethal
4 model here. And you can see that either a single or
5 two doses of the vaccinia vaccine nearly or completely
6 protects the animals against viremia.

7 Shown on the right panel here, these are
8 antibody responses against lethality here, where even a
9 single prime dose of the vaccine protects most of the
10 animals from the lethal outcome. And then the footpad
11 swelling here, almost complete protection. Then the
12 viremia data shown at the bottom, almost complete
13 protection.

14 So, this is an example of what's been seen
15 with many other alphavirus studies over the years,
16 where John Roehrig and colleagues at the CDC actually,
17 in the 1980s and '90s, showed for Venezuela equine
18 encephalitis and other alphavirus that non-neutralizing
19 antibodies can protect very effectively in mirroring
20 models for disease. This study did not delineate
21 whether the protection was absolutely attributed to

1 non-neutralizing antibodies. But that's certainly the
2 simplest explanation.

3 So, moving on now to macaque antibodies. This
4 is a study done -- the initial description of the VLP
5 vaccine, where a macaque -- I believe this was a rhesus
6 macaque that was vaccinated by the VLPs. I believe it
7 was two doses -- was then bled, and serum from that
8 animal was transferred into the IFNAR mouse model here.
9 And then, after challenge, you can see viremia. I
10 believe this is day two where it's more or less the
11 peak following challenge of these mice.

12 You can see that the transferred animals had
13 complete protection against viremia and also against
14 the fatal outcome in this model. And these are the
15 amounts of antibody used. Unfortunately, this paper
16 does not describe the antibody titers in these animals
17 in neutralizing 50 or 80 percent endpoints for post-
18 transfer titers in these animals. I'm not sure if
19 subsequent studies with this vaccine have determined
20 titers like that.

21 This is an example of some work done with

1 human sera by a group at the Pasteur institute in
2 Paris. In this case, they obtained a large number of
3 donors from the post-outbreak period in La Reunion
4 Island in the Indian Ocean in about 2005 and 2006.
5 These are the criteria they used for enrolling patients
6 in this study and obtaining their plasma, so they had
7 to have had a clinical episode including arthralgia,
8 which indicated chikungunya virus infection.

9 They had to have an absence of chronic
10 arthralgia, so by the time they were enrolled, it was
11 at least six months post-acute period and a lack of
12 chronic arthralgia. And then they were given the
13 opportunity to donate plasma. And a product was
14 manufactured from that pooled plasma that's called
15 CHIKVIg, shown here. And then, they also took three
16 individuals and tested their plasma, also by passive
17 transfer.

18 So, Patient A shown here is a non-chikungunya
19 patient. This patient had no clinical signs or
20 symptoms of chikungunya and no testing to indicate past
21 chikungunya infection. Then, they took two other

1 patients that had different kinds of immune responses.
2 Patient B, you can see, had a very high ELISA titer
3 here of about 2000, but a relatively modest
4 neutralizing antibody titer of 40 at an 80 percent
5 endpoint. Then the other patient, C, had kind of the
6 inverse. They had a little bit weaker ELISA titer, but
7 a stronger neutralizing titer of 320. And then there
8 was a negative control here of normal immunoglobulin,
9 and then they tested this manufacturer pooled product
10 as well.

11 So, these are some of the results from their
12 work here where they transferred these plasma or this
13 product into, again, the IFNAR knock-out mouse model.
14 So, the animals were injected IP with a half a mL of
15 one of these two plasmas or 25 milligrams of the
16 purified manufactured product. Then, they were
17 challenged with various doses of wildtype chikungunya.
18 And you can see that, at a low dose here, they started
19 with only 10 plaque-forming units. They had complete
20 protection in all of the immune products, either plasma
21 B or C from the infected people or the pooled product.

1 There was complete protection.

2 But when they started to increase the dose of
3 challenge, eventually they saw a little bit of
4 breakthrough from that protection with the very highest
5 doses, which were up to 10^6 plaque-forming
6 units. Shown here are some of the results for the
7 titration of the plasma into the mice. So, if you do
8 further dilutions like I showed you a few slides back,
9 you eventually start to lose protection from the fatal
10 outcome here.

11 And then they also looked at viral loads in a
12 number of different organs and tissues. In this case,
13 they only use the manufactured immunoglobulin product
14 and then two negative controls, PBS or a sham-
15 manufactured (phonetic) product here called Tegeline.
16 And you can see that they had a major reduction in
17 viral loads in all four of these sites early, following
18 challenge.

19 These are additional data with the same
20 products in the immunocompetent young mouse model. So,
21 in this case, they used black 6 mice but a number of

1 different immunocompetent mouse strains at a young age.
2 Usually up to about three weeks of age, they develop
3 viremia, they develop inflammation of the muscles and
4 joints, changes in their movement, and so forth. So,
5 when they use this model, they obtain very similar
6 results.

7 You can see that they had, with their pooled
8 product or those two chikungunya immune plasmas, they
9 had protection against fatality in this model. And
10 then they titrated out those immune plasma and showed
11 that the protection titrated out as well. And then
12 again, looking at viral loads in various organs and
13 tissues, they showed a reduction in most of those with
14 either the two immune sera or the pooled immune
15 product.

16 This is a study looking at transfer of a human
17 monoclonal antibody that was developed from B cells
18 from infected patients. So, this was, again, tested
19 using a mouse model. In this case, in immunocompetent
20 C57 black 6 mice. These mice were administered either
21 50 or 100 micrograms of that monoclonal antibody, which

1 was purified, or an isotype control. Then, they were
2 challenged with a subcutaneous inoculation of the
3 footpad. This dose was 10 to the 3 focus-forming
4 units.

5 And I won't go into the details here, but
6 using different timings of administration of the
7 antibody or different timings of challenge, they showed
8 a significant reduction in viral loads in both the
9 inoculated footpad site or the contralateral site
10 measuring ankle swelling in all of these mouse models.
11 So, this monoclonal antibody also protected against
12 replication in this model.

13 And then they also looked at antibody
14 concentration in the animals after administration of
15 two doses. By days one and three, shown by the arrows
16 here, you can see that the antibody titers rise at one
17 day after the first administration, and then they rise
18 further after the second administration. And that's
19 two different doses that they used here, 5 and 15 mgs
20 per kg.

21 Then, they looked at a viral load following

1 challenge of these animals. And you can see that they
2 only administered the antibody on day one. But by day
3 two, there was a major drop in the viremia titer that
4 continued for the remainder of the one-week study with
5 a couple of slightly positive samples at these time
6 points, but a major reduction in viremia was attributed
7 to this antibody administration.

8 Then, they did similar studies in rhesus
9 macaques here. So, what I'm showing you here is a
10 transfer of the same monoclonal antibody, followed by
11 assays of a variety of different organs after sacrifice
12 on day 7 after challenge. And you can see that, for
13 nearly all of the organs and tissue sampled, compared
14 to the control antibody -- the one in black here at the
15 top, not a chikungunya antibody -- the two different
16 doses of the chikungunya antibody significantly reduced
17 viral loads almost everywhere in the macaques.

18 So, I want to finish up just by mentioning
19 some of the limitations of these studies which you've
20 already been discussing. The first is lack of
21 quantification of the post-transfer neutralizing

1 antibody titers. It's unfortunate that, in many of
2 these studies, at least the published data include
3 other measures of antibody concentration, but not the
4 kind of gold standard traditional typically plaque
5 reduction, or more recently sometimes, viruses
6 expressing reporter genes used for these assays. But
7 some of them don't include any measures of the antibody
8 titer in the animals immediately before challenge.

9 Now, as was already discussed, a lot of
10 different kinds of neutralization assays are being used
11 these days. Traditionally, plaque reduction
12 neutralization with either an attenuated or wildtype
13 virus strain and 80 or 50 percent endpoints, but many
14 different kinds of assays being used now without the
15 ability to reliably extrapolate between them.
16 Variation in the challenge strain -- often, these
17 studies use only one challenge strain, which is often
18 the La Reunion strain or another strain from the Indian
19 Ocean outbreak. Not very many of them use a strain now
20 circulating in the Americas.

21 And back to the issue of antigenic variation

1 in chikungunya, it's quite limited if you do
2 traditional comparisons of one lineage of chikungunya
3 antisera from the same lineage tested against other
4 lineages. There's only slight variation in titers,
5 usually about two to four-fold. But nevertheless,
6 there are significant differences in virulence and
7 possibly in pathogenicity. For example, the strain
8 that arrived in the Caribbean in 2013 from Asia appears
9 to be quite less virulent for producing chronic
10 arthralgia in people than the strain that hit the
11 Indian Ocean basin and then moved into Asia around
12 2005-2006.

13 And then, finally, the endpoints used for
14 these studies varied quite a bit. A lot of them used
15 the same IFNAR mice or closely related strains with the
16 same knock-out, and lethal endpoints as well as this
17 footpad swelling model. But even the macaque studies,
18 often they don't report fever at all. Only a few of
19 them report joint swelling and other measures of
20 inflammation. And most of those involved very high
21 doses of the virus, which kind of brings me to some of

1 the issues that I thought would be important for
2 discussion.

3 So, for non-human primates, what are the most
4 appropriate indications of disease and endpoints to be
5 used? And what's the best dose to use? So, typically,
6 a mosquito inoculates less than one thousand plaque-
7 forming units during a transmission event into a human.
8 Yet, those very low doses are rarely used in efficacy
9 studies. Typically, they're at least a ten or a
10 hundred-fold higher. Sometimes, up to 10 to the 7 or 8
11 or higher, as you probably heard this morning, which
12 seems to increase the ability of the virus to cause
13 joint pathology in the animals. But on the other hand,
14 it's a very unnaturally high dose.

15 So, where's the tradeoff and the right balance
16 there? Do we need to look at additional chikungunya
17 virus strains, or is the virus conserved enough that
18 one strain is sufficient? I think, for the antigenic
19 variation, I have no concern that one strain is not
20 enough. But I think that potentially for the
21 pathogenicist mechanisms, there could be minor

1 differences that might need to be considered.

2 And then, is there sufficient variation in
3 human neutralizing antibody responses that, when we
4 pool their sera or when we pool mouse sera or macaque
5 sera, are we masking that animal-to-animal variation
6 that could be affecting the ability to use neutralizing
7 antibodies as the predictor of protection? I think
8 this is probably unlikely. I think the epidemiologic
9 data from the Philippines suggests that it's not a
10 major factor.

11 Although a very small number of human sera
12 were used in that study I just showed you, the two sera
13 that had the divergent responses in neutralizing versus
14 total antibody titers, both of those had no problem
15 protecting the animals. But this is certainly
16 something that needs to be discussed going forward.
17 So, thanks for your attention.

18 **DR. EL SAHLY:** Thank you, Dr. Weaver. Any
19 questions from the committee? Dr. Fischer.

20 **DR. FISCHER:** One question that may not be
21 relevant here since all the manufacturers here

1 presented neutralizing data, but what would be the
2 potential mechanism of protection of non-neutralizing
3 antibodies?

4 **DR. WEAVER:** I think there's not a good answer
5 to that question, even today. Probably binding to
6 virus, limiting dissemination, perhaps, in some way.
7 But I don't think anyone's really worked out specific
8 mechanisms for that.

9 **DR. EL SAHLY:** Mr. Toubman?

10 **MR. TOUBMAN:** Just near to the last point
11 there about using unreasonably high doses that elicit
12 signs of disease in animals. And basically, one of the
13 manufacturers presented that they were able to produce
14 joint inflammation. But are you suggesting that maybe
15 that was only possible because of extremely high doses,
16 which you would not see in normal --

17 **DR. WEAVER:** Well, I think -- so, in our
18 experience, we've done a few studies in cynomolgus
19 macaques. Our doses are typically 10 to the 4 or 10 to
20 the 5, which is a little bit higher than a natural dose
21 but not as high as some of these studies. We've never

1 been able to detect any joint swelling in our control
2 animals following a challenge. We've also looked using
3 telemetry reductions in movement of the animals in the
4 cage, and never been able to detect any significant
5 change in unprotected animals. We haven't used these
6 higher doses on our own studies.

7 I'm sure Dr. Roques could comment more about
8 this. He's done a lot more variation in challenge
9 doses. We were talking over lunch; he was commenting
10 about these macaques. No matter what you do to them,
11 they don't slow down.

12 **DR. EL SAHLY:** Additional questions to Dr.
13 Weaver? Thank you, Dr. Weaver. Last but not least,
14 Dr. Sudhakar Agnihothram. Sorry if I mispronounced
15 your name.

16 **DR. AGNIHOTHRAM:** No, you did it right.

17 **DR. EL SAHLY:** I did? Okay. He's a biologist
18 at the Office of Vaccines and Related Research at the
19 FDA. He will give an FDA presentation on the matter.

20

1 **FDA PRESENTATION**

2

3 **DR. AGNIHOTHRAM:** Good afternoon, everyone.

4 Thanks for staying through my talk. Now that we heard
5 interesting thoughts on several aspects of chikungunya
6 disease, including epidemiology, disease transmission,
7 animal models, passive transfer studies, my talk is
8 going to focus on the approaches to assessing
9 effectiveness of chikungunya vaccines. And what are
10 the factors that one needs to consider while utilizing
11 these approaches?

12 Here is the brief overview of my talk.
13 Initially, I'll be discussing the regulatory framework
14 for endpoints to assess vaccine effectiveness, where
15 I'll be talking about effectiveness endpoints in the
16 context of licensure pathways.

17 Please note that discussion of a specific
18 licensure pathway for chikungunya vaccine is beyond the
19 scope of this VRBPAC, and the committee will not be
20 asked to discuss licensure pathway of chikungunya
21 vaccines. Then, I'll be talking about clinical disease

1 endpoint efficacy trials and factors that influence
2 feasibility of conducting field efficacy trials.

3 I'll then be transitioning to the second
4 portion of my talk where I'll be talking about
5 approaches to identify an immune marker reasonably
6 likely to predict protection from chikungunya virus
7 infection and disease. And such approaches will
8 include sero-epidemiological studies and non-human
9 primate studies. Finally, I'll be wrapping up by
10 reemphasizing the topic for today's VRBPAC discussion.

11 To support licensure through the traditional
12 approval pathway, vaccine effectiveness may be
13 demonstrated by using a clinical disease endpoint or
14 the biomarker. For example, immune response that is
15 scientifically established to predict protection
16 against chikungunya infection and disease. Other
17 approval pathways are also available for certain
18 diseases or scenarios.

19 The first one is the accelerated approval
20 pathway. To support licensure through the accelerated
21 approval pathway, vaccine effectiveness may be

1 demonstrated using a surrogate endpoint -- for example,
2 immune marker -- that's reasonably likely to predict
3 clinical benefit. Now, in this case, that would be
4 protection from chikungunya disease.

5 There is also animal rule approval pathway.
6 Now, to support licensure through the animal rule
7 approval pathway, vaccine effectiveness may be
8 demonstrated using a disease endpoint in a relevant
9 animal model that enables conductive studies to select
10 an effective dose and regimen in humans. Please note
11 that animal rule approval pathway is only available in
12 a situation where licensure through traditional or
13 accelerated approval pathway is not feasible. FDA is
14 not considering the use of animal rule pathway for
15 chikungunya vaccine for the same reason.

16 One also has to note that licensure through
17 both accelerated and animal rule pathways require post-
18 approval confirmatory studies to demonstrate clinical
19 benefit. As I mentioned before, discussion of the most
20 appropriate approval pathway is beyond the scope of
21 this VRBPAC, and the committee will not be asked to

1 discuss licensure pathways.

2 Talking about clinical disease endpoint
3 efficacy trials -- in the absence of a scientifically
4 established immune marker that predicts protection
5 against chikungunya virus infection and disease,
6 traditional approval will require a clinical disease
7 endpoint efficacy trial, which ideally would be a
8 randomized controlled, double-blind trial to
9 demonstrate vaccine effectiveness against virologically
10 confirmed chikungunya virus infection and disease.

11 Now, feasibility of field efficacy trials may
12 be influenced by several factors. For instance,
13 increased scope and frequency of chikungunya outbreaks
14 with high attack rates may allow for field efficacy
15 trials of chikungunya vaccines. However, as we heard
16 from different talks this morning and other
17 discussions, outbreaks may be irregular and
18 unpredictable. And therefore, feasibility of
19 conducting such trials may be uncertain.

20 Now, considerations for feasibility of field
21 efficacy trials also include ensuring that there's

1 adequate infrastructure for conducting such trials, and
2 there's also close monitoring of chikungunya disease
3 activity. Having touched base on the regulatory
4 framework and the clinical disease endpoint efficacy
5 trials, I'm now going to transition to other approaches
6 where one can identify immune markers reasonably likely
7 to predict protection against chikungunya virus
8 infection and disease.

9 The first is sero-epidemiological studies.
10 Sero-epidemiological studies have been proposed as an
11 approach to identify an immune marker reasonably likely
12 to predict protection. Now, prospective sero-
13 epidemiological studies in chikungunya endemic regions
14 could employ active surveillance with serologic and
15 virologic testing methods to identify cases of
16 chikungunya virus infection, with correlation of
17 baseline antibody titers should be neutralizing
18 antibodies against chikungunya virus at enrollment with
19 infection and disease outcomes during the surveillance
20 period.

21 Now, considerations for conductive sero-

1 epidemiological studies to include: reliability of
2 surveillance and testing methods to identify clinical
3 cases that reflect established features of chikungunya
4 disease and epidemiology; reliability of subject
5 recruitment methods to avoid potential selection bias;
6 proper validation of serologic assays to quantify
7 antibody titers, and in many cases, measured immune
8 marker may correlate with, but not be responsible for,
9 protection against chikungunya disease.

10 Second approach is cynomolgus macaque model of
11 chikungunya infection and disease and using this model
12 to predict an immune marker. A non-human primate model
13 of chikungunya virus infection and disease has been
14 proposed to identify an immune marker reasonably likely
15 to predict protection in humans.

16 This macaque model, as we saw in previous
17 charts, recapitulates several features of human
18 chikungunya disease. That includes fever, rash, viral
19 dissemination in tissues, and abnormal blood chemistry.
20 However, uncertainties do exist regarding the relevance
21 of this model to human disease. And they include

1 differences in disease features during subacute and
2 chronic phase that's being observed between the
3 cynomolgus macaques and humans.

4 A challenge dose of chikungunya virus that's
5 representative of natural infection in humans, which is
6 10 to the 3rd plaque-forming units induces fever, which
7 may or may not be accompanied by rash. But there is no
8 overt signs of arthritis. If you go a little higher,
9 higher challenge doses greater than 10 to the 7th
10 plaque-forming units does induce inflammation and
11 effusion in joints, but also results in
12 meningoencephalitis and death in cynomolgus macaques.

13 Talking about a passive transfer of human
14 antibodies to non-human primates using this macaque
15 model to establish an immune marker -- passive transfer
16 of pooled human sera or purified immunoglobulins from
17 vaccines into non-human primates prior to chikungunya
18 virus challenge has been proposed to identify an immune
19 marker reasonably likely to predict protection.
20 Uncertainties regarding the utility of such passive
21 transfer studies in non-human primates do include

1 several factors.

2 First, will an immune marker derived using
3 pooled human serum or purified immunoglobulins that's
4 prepared from this pooled serum accurately predict
5 protection from chikungunya disease in humans? Are
6 there clinically meaningful differences in antibody
7 quality that may influence predictive capacity between
8 a certain titer in a vaccinated human and the same
9 titer resulting from dilution during passive transfer
10 studies?

11 What would be the optimal timing for
12 collecting post-vaccination human serum to be used in
13 passive transfer studies? Now, as we just discussed in
14 previous talks, are there other factors in human serum
15 besides antibodies -- for instance, cytokines -- that
16 contribute to protection against chikungunya virus
17 infection and disease?

18 Having discussed all of this, we request that
19 the committee discuss the following aspects of clinical
20 studies to assess the effectiveness of chikungunya
21 vaccines: feasibility of randomized, controlled

1 clinical disease endpoint efficacy trials; role of
2 sero-epidemiologic data in identifying an immune marker
3 reasonably likely to predict vaccine effectiveness.

4 Second, we also request that the committee
5 discuss the utility of the non-human primate challenge
6 model to assess effectiveness of chikungunya vaccines,
7 including: effectiveness endpoints such as viremia,
8 arthritis-related endpoints, or other essential
9 endpoints; role of passively transferred sera or
10 purified immunoglobulin from vaccinated humans in
11 identifying an immune marker reasonably likely to
12 predict vaccine effectiveness; whether additional
13 information is needed to support the utility of the
14 non-human primate challenge model.

15 Thank you, everyone, for listening. And I'll
16 be happy to take any questions if there are any.

17 **DR. EL SAHLY:** Thank you for the presentation.
18 Dr. Meissner has a question.

19 **DR. MEISSNER:** Yes. I'd like to go back to
20 the issue of safety. Could you make a few comments
21 about how you address safety if you use the non-

1 traditional pathway that is accelerated approval or
2 animal model?

3 **DR. AGNIHOTHRAM:** So, accelerated approval
4 pathway is different from animal model. And if we use
5 accelerated approval to license chikungunya vaccines,
6 pre-licensure studies to assess safety of chikungunya
7 vaccines will still be required. We will be requiring
8 manufacturers to establish a safety database of a
9 certain size.

10 Now, that certain size is on a case-by-case
11 basis and we cannot give a specific number. But
12 typically, it's around three thousand. So, we would be
13 requiring pre-licensure studies to establish safety.
14 Does that answer your question?

15 **DR. MEISSNER:** Yes, although it still becomes
16 complicated. So, that will involve both seropositive
17 and seronegative individuals?

18 **DR. AGNIHOTHRAM:** If there are concerns with
19 use of these vaccines in seropositive individuals,
20 like, you know, that is strong, then yes. You know?
21 That may involve use of both the populations.

1 **DR. MEISSNER:** Thank you.

2 **DR. EL SAHLY:** Dr. Kurilla?

3 **DR. KURILLA:** In your discussion of clinical
4 disease endpoint efficacy trials, you say, in the
5 absence of a scientifically established immune marker,
6 then you'd have to do an efficacy trial traditional.
7 That sort of begs the question, how does the FDA define
8 a scientifically established immune marker? What does
9 it take to do that?

10 **DR. AGNIHOTHRAM:** I guess that's part -- wait,
11 you do this? I guess that's part of the reason this
12 VRBPAC is being convened as well. But it's the
13 reliability of an immune marker in terms of predicting
14 protection against chikungunya infection and diseases.

15 Now, in instances that immune markers are
16 being used in clinical trials, there is a precedent
17 using -- like, you know, previous clinical trials has
18 been established. For instance, in anti-HBs there is
19 surface antigen for licensure of hepatitis vaccines.
20 Well, that's 10 mL infectious units per mL, like was
21 established in Heptavax clinical trial. And then that

1 was also confirmed following up with several
2 observational studies.

3 Now, for this, we all agree that there's no
4 scientifically-established immune marker. But
5 depending upon what features of the -- what
6 manifestations of the disease are being presented by a
7 specific antibody titer, that could be one parameter of
8 defining an immune marker, which obviously has to be
9 confirmed in post-licensure studies.

10 **DR. KURILLA:** Just to clarify, can you
11 actually have a scientifically established immune
12 marker in the absence of a previously licensed vaccine?

13 **DR. AGNIHOTHRAM:** Using sero-epidemiological
14 studies -- if the data from the sero-epidemiological
15 studies are authentic enough, and then if they are
16 convincing, then an immune marker derived using sero-
17 epi studies could serve as a scientifically established
18 immune marker.

19 **DR. EL SAHLY:** Dr. Fink?

20 **DR. FINK:** Yeah, so, maybe I can clarify a bit
21 further that I think what you're implying -- and this

1 is correct -- is that, typically, validation of an
2 immune marker as a scientifically established surrogate
3 marker that predicts protection against disease would
4 be accomplished in the context of a clinical endpoint
5 efficacy study that definitively shows efficacy of the
6 vaccine and that examines immune responses among cases
7 and non-cases and then proceeds through a rigorous,
8 statistical analysis to derive that immune marker.

9 I guess one could imagine a scenario in which
10 that sort of process takes place. And before the
11 vaccine actually undergoes licensure, there's an
12 agreement on an immune marker that is scientifically
13 established. But typically, that's not the case. But
14 just to be very clear, we're not asking the committee
15 to weigh in on an established immune marker for
16 chikungunya disease.

17 **DR. EL SAHLY:** Dr. Gruber.

18 **DR. GRUBER:** I just wanted to add to this a
19 little bit. First of all, I agree completely with what
20 was just said. This one thing -- and I think that it's
21 maybe a little bit confusion here when we use these

1 terms of surrogate and correlative protection and
2 immune marker -- I just wanted to clarify, and perhaps
3 it's already clear to the committee, but under these
4 accelerated approval pathways, the marker is not -- it
5 doesn't have to be a well-established marker. There's
6 reasons why the regulations say it's reasonably likely
7 to predict protection.

8 So, there is some residual uncertainty then as
9 to the capacity or capability of that biomarker, really
10 to predict protection, which is exactly the reason why
11 if we approve a vaccine based on such marker, the
12 company is then required to confirm the clinical
13 benefit post-licensure.

14 So, there's a big difference here. And these
15 well-established markers are -- you know, one was
16 mentioned. Then you can think about it anti-tetanus
17 antibodies, anti-deferring antibodies, these are these
18 -- oh, anti-hep titers. Okay, but this is a very
19 different category than what we're talking about under
20 the accelerated approval pathways. There's always
21 uncertainty as to the biomarker really predicting

1 benefit.

2 **DR. KURILLA:** But also, those markers that
3 you're using for accelerated approval may be specific
4 for each vaccine. And it may differ from vaccine to
5 vaccine.

6 **DR. GRUBER:** Absolutely. Yes, that's true.

7 **DR. EL SAHLY:** Dr. Fischer?

8 **DR. FISCHER:** Thank you. I have a question
9 regarding the sero-epidemiologic studies. So, when
10 comparing, to let's say, a vaccine clinical efficacy
11 study, I understand you would not have the issues
12 related to the enrollment, the vaccination, the safety
13 follow-up. But you still would need to identify cases
14 in order to define the baseline we saw, evidenced of
15 two studies here.

16 Other than those factors of having to do the
17 randomization, vaccination, safety follow-up, what
18 makes a sero-epidemiologic study to establish the
19 marker more feasible than the vaccine clinical study?
20 You still need to find a population where you're going
21 to have cases accrue to define that marker.

1 **DR. AGNIHOTHRAM:** What makes a sero-
2 epidemiological study easier than conducting a
3 randomized controlled clinical trial? Because, I
4 guess, sample size is one aspect. You know, for a
5 sero-epidemiological study that -- I mean, you do not
6 have a predefined success criteria in the sero-
7 epidemiological study to define the perfect antibody
8 titer, for instance. Now, sero-epi studies are mostly
9 aimed at identifying a marker that is predictive of
10 protection. And the census criteria as not like, you
11 know, predefined with the sero-epi study, whereas with
12 the randomized control, you do have to have a
13 reasonable amount of a sample size to define a census
14 criteria.

15 **DR. EL SAHLY:** Maybe the calculation is
16 different. However, the expectation for a large number
17 of volunteers and large number -- well, a long duration
18 and sufficient number of cases accrual is very similar.

19 **DR. JANES:** Hana, may I weigh in? I would
20 agree. Roughly speaking, a sero-epidemiologic study
21 would ideally consist of a prospective study that

1 identifies a cohort of at-risk individuals and collects
2 specimens on those individuals at enrollment, and then
3 follows those individuals, some of whom ultimately
4 become infected so that the data can be used to
5 evaluate the extent to which various immune responses
6 measured in the specimens taken at baseline predict
7 individuals' risk of infection.

8 And so, an adequately powered study would
9 require a sufficient number of infections in that
10 cohort to establish reliably a biomarker as a correlate
11 of risk. And yet, I think we've been presented today a
12 couple of existing seemingly well conducted studies
13 that have been of that nature that have enrolled a
14 cohort of individuals and collected specimens, and
15 enabled the immune responses measured in those
16 specimens to be correlated with risk.

17 So, roughly speaking, the advantages relative
18 to a randomized trial or the logistical simplicity
19 relative to randomized trial is that you are enrolling
20 a fixed cohort, none of whom -- the individuals are not
21 vaccinated. So, you need fewer such individuals than

1 to do a randomized trial where you have both vaccinated
2 and the unvaccinated individuals. But conducting a
3 cohort study in a population with low incidence still
4 is challenged with the need to get sufficient cases for
5 analysis.

6 **DR. EL SAHLY:** Dr. Fink?

7 **DR. FINK:** Yeah. So I agree very much with
8 the points that were just made. I guess what wasn't
9 well stated in the question but, I guess, should be
10 obvious is that there have been no vaccine studies
11 conducted today. And there have been two sero-
12 epidemiologic studies that we've heard about.

13 Ultimately, the acceptability of -- or the
14 adequacy of those two studies to inform identification
15 of an immune marker reasonably likely to predict
16 protection rests on the details of how those studies
17 were conducted. And that's something for us to look
18 at. But we would really appreciate the committee's
19 discussion and advice on what would be important
20 features of such studies to inform their adequacy.

21 **DR. EL SAHLY:** Okay. Thank you. I think

1 there's a lot to be said, that remains to be said. We
2 will -- oh, Dr. Pergam, are you on the line? I always
3 forget.

4 **DR. PERGAM:** Yeah, I'm on the line. I'm fine.
5 No additional questions from me.

6 **DR. EL SAHLY:** Oh, okay. But just to remind
7 you and remind everyone, after the 10-minute break we
8 will be deliberating all these issues along the lines
9 of the two questions posed by the FDA. Thank you. So,
10 ten minutes, that means 3:22. Thank you.

11

12 **(BREAK)**

13

14 **COMMITTEE COMMENTS**

15

16

17 **DR. EL SAHLY:** We are reconvening for the
18 committee's comments on the two questions as presented
19 by the FDA. We will begin by discussing question
20 number one.

21 Question number one has two sub-questions

1 within it. I'm going to ask that individuals around
2 the table provide feedback around those two sub-
3 questions within it back to back. Item one, discuss
4 the following aspects of clinical studies to assess
5 effectiveness of chikungunya vaccines: a) feasibility
6 of randomized controlled clinical disease endpoint
7 efficacy trials and, b) the role of sero-epidemiologic
8 data in identifying an immune marker reasonably likely
9 to predict vaccine effectiveness. We will go a bit out
10 of order. Dr. Geeta Swamy is going to discuss first,
11 give her opinion.

12 **DR. SWAMY:** I guess I just have a couple of
13 comments. I think clearly the difficulty -- many
14 things have been raised about feasibility and the
15 efficacy is the disease incidence and the
16 predictability. If there are ways to have sort of
17 preparedness to be ready for outbreaks and to really
18 focus in on the areas where we have endemic disease, I
19 think it may still be feasible but long term and a
20 significant investment, obviously. I'm going to
21 probably defer to other colleagues on the sera epi data

1 because I don't know that we've seen enough to know
2 that we can use the immune markers right now to be able
3 to predict that.

4 **DR. EL SAHLY:** Okay. Thank you, Dr. Swamy.
5 Dr. Gans?

6 **DR. GANS:** Thank you. I would agree with the
7 comment on the first that, given that we are unsure
8 about some of the animal components and using other
9 models, a randomized controlled trial is obviously the
10 best. We understand the difficulty around the
11 epidemiology of this. So I think there are some ways
12 of working in studies to work around that. The sero-
13 epidemiology I think is embroiled in the same sort of
14 questions around being able to identify a large enough
15 number of cases. So I think they're embroiled
16 together. And I think if one is not feasible, probably
17 the other is not.

18 **DR. EL SAHLY:** Okay. Thank you. Dr.
19 Bollinger? Am I saying it right? Bollinger or Bollin-
20 gur?

21 **DR. BOLLINGER:** It depends on who you talk to

1 in my husband's family. Dealer's choice. You can call
2 me either. I certainly think that there are
3 feasibility issues around this, and also I think the
4 different presentation of the disease, depending on the
5 outbreak and patient to patient variability, makes
6 assessing the clinical impact of this vaccine difficult
7 as well. I do think that it is important to not always
8 assume an RCT is the only way to gather reliable data.
9 And sometimes, we do have to leverage data from
10 multiple sources to be able to establish safety and
11 efficacy. So if, indeed, it turns out that this is not
12 feasible to study in a randomized controlled trial, I
13 think it is a very reasonable option to look at data
14 from other sources with, of course, post-marketing
15 requirements to further establish especially safety.

16 **DR. EL SAHLY:** Thank you. Dr. Fischer?

17 **DR. FISCHER:** Thank you. So I think we heard
18 a lot of very promising data with regard to the
19 evidence that there could be a good immunologic
20 surrogate or correlate of protection with neutralizing
21 antibodies being the most likely candidate. However,

1 regarding the feasibility of a randomized trial, I
2 think that most of the presentations just focus on
3 chikungunya as an outbreak prone disease, which it
4 certainly is. And that is where the most attention
5 occurs. But I think we ignore the endemicity or the
6 endemic background disease that occurs. And I think
7 there are studies out there, at least two of which were
8 referred to here from Tanzania and from Southeast Asia,
9 that suggest there are significant numbers of people,
10 children in particular, who have disease that is picked
11 up in studies that are done looking for dengue that
12 potentially make randomized controlled trials feasible,
13 although difficult. And identifying those locations
14 would be difficult.

15 With regard to the sero-epidemiologic data, I
16 think it also is caught up in the same issues as was
17 referred to. And I think the two studies that have
18 already been done, which FDA would evaluate, have
19 certain limitations. One of them, for example, was
20 done in children only; whereas, the vaccines primarily
21 are being focused for adults. Whether or not there

1 would be differences in the correlate of protection in
2 different age groups would need to be assessed whether
3 those would provide a -- and then, I think the non-
4 human primate studies certainly show a lot of promise,
5 especially with regard to an outcome of viremia. I'm
6 less convinced that it could be used as a model for an
7 outcome of clinical disease endpoint from what we've
8 seen.

9 **DR. EL SAHLY:** Thank you, Dr. Fischer. Mr.
10 Toubman?

11 **MR. TOUBMAN:** So the problem with the
12 question, frankly, is that the word feasible is not
13 defined, and that's why my questions for the companies
14 was based upon different ways of asking the question.
15 Take cost out of it or include cost. I think if we do
16 take cost out of it, it is feasible. It's difficult,
17 but it can be done. You pick a bunch of sites, and
18 it's waiting and watching and seeing what happens. I
19 did hear from Dr. Powers that the incidence between the
20 recurrences is lessening. So in fact, it might not be
21 such a long wait after all. So there might be an

1 advantage there. So from what I heard, it's feasible
2 but difficult, or as one of the companies said in their
3 presentation it was limited feasibility. But it's
4 feasible.

5 But if you factor in cost, which is to say are
6 these companies willing to do it, they don't have to do
7 it. It's their choice. I think two of them clearly
8 said, "No, we won't do it." The other two was more --
9 they were hedging a little bit. And frankly, I think
10 there's a -- obviously, I don't know this stuff at all.
11 But from what other people are saying and what I have
12 read. The randomized controlled study, there's a
13 reason for that. The RCT is there for a reason, so you
14 don't pass over it unless it's really, really
15 necessary. And I think we should recognize that,
16 compared to so many other diseases, this is a serious
17 disease. The people who get it, it's very
18 debilitating.

19 And I certainly honor the people like Dr.
20 Roques who has worked on this -- spent years working on
21 it and trying to find an answer. We need an answer.

1 But in light of the fact it's basically a non-fatal
2 disease. It's a disease that doesn't result in
3 permanent disability, long-term sometimes but not
4 permanent. On balance, is this a case where you should
5 wave that absolutely critical requirement? And I'm not
6 sure it is.

7 **DR. EL SAHLY:** Thank you, Mr. Toubman. Dr.
8 Wharton?

9 **DR. WHARTON:** I did the wrong thing. Thank
10 you. This is a really interesting problem. And it is
11 very striking to me that, apparently, speaking of
12 feasibility, it's more feasible to develop multiple
13 chikungunya vaccines than it is to actually develop an
14 understanding of the epidemiology of the disease, its
15 natural history, and its pathogenesis. Because that's
16 sort of the unknown space we're in where the technology
17 for these potential preventative measures is much
18 farther along than some basic understanding that you
19 would hope we would have before we would be having to
20 have conversations like this. But we're where we are.
21 And it does seem not feasible to me to expect that

1 there would be randomized clinical -- a randomized
2 controlled clinical disease endpoint efficacy trials.
3 I think that's not going to happen. And it does seem
4 likely to me that there could be a laboratory endpoint
5 that was reasonably likely to predict protection.

6 In terms of collecting this through sera --
7 through a sero-epidemiological study -- I think that
8 could be done. Whether or not that would be done I
9 don't know. It does seem like this is a disease that
10 our understanding of is really -- has not had an
11 adequate level of investment so that some of these
12 basic questions are answered. And if there was a study
13 site, study platform developed where actually some kind
14 of longitudinal population work was being done, it
15 seems like this would be a kind of straightforward
16 thing to do if it was in an endemic area and assuming
17 that the laboratory work is standardize enough to do
18 that. So it seems like that might be possible if there
19 was an appropriate setting. Are we doing both
20 questions at once? Just number one? Okay. So I'm
21 done.

1 **DR. EL SAHLY:** Dr. Kurilla?

2 **DR. KURILLA:** Yes, so I think -- I mean, we've
3 had a lot of discussion on the feasibility of a
4 randomized controlled clinical disease endpoint
5 efficacy trial. And I'm of the opinion that this is
6 not feasible. I think in the context of an outbreak it
7 is potentially doable, but I don't see that as
8 something that individual corporate entities are going
9 to be in a position to establish that capability
10 globally to be able to jump on top of any outbreak. I
11 think that that's something that's more in the context
12 of post-licensure where individual entities, non-profit
13 entities, foundations, governments would be more likely
14 to establish that resource and capability so that the
15 companies would be able to feed into that going
16 forward. So I really don't see the feasibility of an
17 RCT in this context.

18 For the sero-epidemiologic data, I think it
19 does have quite -- it has some of the similar
20 limitations that the RCT has. On the other hand, I
21 think in the context of a lot of -- just straight

1 epidemiological research, as was pointed out, it's very
2 limited. That will certainly be a little more -- there
3 will be more opportunity for that. But I don't see it
4 as being definitive in terms of coming up with an
5 immune marker. I see it coming up with the list of
6 candidates. It could be evaluated in other types of
7 studies. And it will bound the problem quite a bit and
8 will point people in the right direction into what
9 range you need to be for maybe alternative methods of
10 licensure.

11 **DR. EL SAHLY:** Thank you. Dr. Spearman?

12 **DR. SPEARMAN:** Thank you. I want to echo
13 something that Dr. Meissner said that the vaccines
14 themselves are just really fantastically exciting. So
15 it's great technology. So in terms of answering this
16 question, I don't claim to be an expert in this
17 particular virus or its epidemiology. But from hearing
18 what we heard today I'm left wondering if there really
19 have been adequate prospective sero-epidemiologic
20 studies in endemic regions that we really know how this
21 virus spreads after the intense epidemics that seem to

1 die out. So I was a little bit confused by the
2 southern Thailand data where it looked like there's
3 ongoing transmission, perhaps. Is that happening in
4 other parts of the world? And would that make a
5 randomized clinical trial more feasible if you could
6 identify how much of that is really happening?
7 Certainly, the complexities of the individual --
8 identifying where the next epidemic's going to be would
9 make it not feasible if that's all there is. But I'm
10 not convinced there's been a lot of prospective or
11 active epidemiology for this disease.

12 The antibody data from animal models looks
13 fantastic. That's about as good as you could ever get
14 for antibody mediated protection. So from the animal
15 models, it's wonderful. I'm less convinced from the
16 limited amount of human data we've seen that we could
17 say there's newts correlate with being protected. I'd
18 like to see a lot more on that before we could really
19 comment on that. So is it feasible to do an RCT? I
20 think we need more understanding of how the virus is
21 spread and more data from active surveillance. So

1 getting there seems to be really important to make
2 these kind of decisions.

3 **DR. EL SAHLY:** Thank you, Dr. Spearman. In
4 view of the question of feasibility, built in the
5 question of feasibility is, again, an understanding of
6 the epidemiology. We're going. It's mine turn. Built
7 in is the knowledge of the issue of what's happening
8 with the epidemiology. The data at least from the --
9 if we were to take the data from the Philippines, 850
10 individuals followed for a year, we accrued 105 cases.
11 That makes it feasible, but how representative are
12 these data? We do not know.

13 Some of it was subclinical, so that has to be
14 taken into account, meaning creative ways of getting at
15 disease efficacy has to be built in. So the kind of
16 data from the Philippines makes it seem feasible. When
17 we see these spikes from Colombia and other places, it
18 makes it seem maybe not feasible. Although, these
19 individuals were picked only when there's an outbreak.
20 No one was actively doing surveillance on them. So I
21 can't quite answer comfortably regarding feasibility in

1 the absence of epidemiologic data.

2 To the issue of sero-epidemiologic data, it
3 seems that also a large number of individuals will have
4 to be enrolled and followed for a long time if we are
5 to believe that chikungunya is not circulating at some
6 background level we're not detecting because of the
7 design of the studies that get published. So the
8 feasibility of a particular sero-epi clinical study
9 sort of follows the same pitfalls in terms of our
10 knowledge of what's happening epidemiologically with
11 chikungunya. But it would certainly enrich sort of
12 feature clinical trials in that domain.

13 I'm going to ask Dr. Pergam so I don't forget
14 him. Dr. Pergam? Okay. We will circle back again.
15 Dr. Meissner?

16 **DR. PERGAM:** Sorry. I'm here. I apologize.
17 I have to change my mute status. So is it okay if I go
18 ahead?

19 **DR. EL SAHLY:** Yes, please.

20 **DR. PERGAM:** Okay. Great. So I at the moment
21 am in sort of general agreement with colleagues who've

1 spoken so far. I think one thing to keep in mind is
2 what's challenging about delaying possible vaccine
3 approval is that there are still large areas of the
4 world that are potentially at risk for developing
5 chikungunya. And not having a vaccine available would
6 potentially put additional patients at risk if we did
7 feel like there was a potential benefit to the vaccine.

8 I think one thing that was a little bit
9 interesting that you didn't discuss was the mortality
10 associated with chikungunya. While we normally think
11 about this as a benign disease, in high risk patients,
12 elderly patients and the really young, the rates that
13 are reported are one in a thousand, which is equivalent
14 to what we see in measles. So I think that's important
15 to keep that in context as we're thinking about this.

16 At the same time, I think the feasibility of
17 these trials seems quite challenging, partially because
18 we just don't have enough data about ongoing
19 transmission in areas where chikungunya has sort of had
20 its original spike and is sort of endemic in those
21 areas. I think from what I've seen from the data is

1 most of what has been collected is during an acute
2 event. And there's only been a few areas where they've
3 continued to collect data afterwards. And I still
4 think probably the place that was most intriguing was
5 the data from Brazil where they had sort of a general
6 decrease in cases but then, over the past few years,
7 they've started to see an increase in cases again. It
8 would suggest that in areas where the disease has
9 become endemic there still could be opportunities to do
10 a randomized clinical trial.

11 And I think in any vaccine, I think we need to
12 be really cautious, particularly with newer vaccines
13 and methods for how these are developed for doing good
14 rigorous studies. So I'm torn between -- sort of stuck
15 between a rock and a hard place in terms of the ability
16 to do these kinds of trials and the challenges that it
17 takes to enroll a large number of patients, wanting to
18 get them done quickly, and also the challenges of being
19 unable to determine where these locations -- the virus
20 will show up again. I think the sero-epidemiologic
21 studies do seem interesting, but I'm still struggling a

1 little bit because of the data that was presented. The
2 differing rates of serologic responses in the different
3 strategies in how this is assessed in different
4 studies, I just don't feel like we have enough data to
5 be able to make a clear distinction about where and
6 what would be the specific cut off that we feel
7 comfortable with.

8 **DR. EL SAHLY:** Thank you, Dr. Pergam. Dr.
9 Meissner?

10 **DR. MEISSNER:** Thank you. I don't like
11 answering this after Dr. Wharton because I have so much
12 respect for her experience with vaccines. I was a
13 little surprised at what you said, I must say. Once a
14 vaccine is licensed, it will not be studied
15 effectively. There will be phase four trials, but it
16 will not be the same reliable information that we get
17 before licensure. And I guess the most important issue
18 is the safety issue. You could argue, if it didn't
19 work very well, that would be okay as long as it didn't
20 cause harm. I don't think we know that yet.

21 Now, as Dr. Gruber said, I'm sure the FDA will

1 require sufficient numbers to demonstrate safety. I
2 don't know what that number will be. It will have to
3 be in seropositive, seronegatives. It will have to be
4 in different age groups. I don't know if there are
5 genetic predisposition among different groups to
6 arthritis or arthralgia. It just seems to me that
7 there are an awful lot of unknowns. But again, I'm
8 very, very sympathetic to the pharmaceutical companies
9 that are making their presentation today. If it comes
10 down to either licensing the vaccine at this stage or
11 not having a vaccine, that's the question I hope that
12 we're talking about.

13 **DR. EL SAHLY:** Next meeting on that.

14 **DR. MEISSNER:** Okay. But I think of the
15 rotavirus, very different vaccine, but there were over
16 70,000 subjects enrolled over how many years? It was a
17 very, very expensive trial. It delayed the
18 availability of the vaccine, which is something that
19 hasn't been mentioned too much. That is, if a long
20 trial is conducted, then people will not have the
21 benefit or the supposed benefit of this vaccine.

1 So it's hard. But given our uncertainty
2 around chikungunya -- and there really isn't another
3 alphavirus that I can think of which we can draw some
4 understanding. So I have a little bit of difficulty
5 with using a serologic correlate, and I don't think
6 there's an animal model. Thank you.

7 **DR. EL SAHLY:** Thank you, Dr. Meissner. Last
8 but not least, Dr. Janes.

9 **DR. JANES:** Am I last? So I'll try to keep
10 mine brief. I agree in large part with much of what's
11 been said. It's clear that a randomized controlled
12 trial is ideal for getting a reliable estimate of the
13 efficacy of a vaccine. Personally, I don't feel like
14 I'm there in terms of being convinced of the
15 infeasibility of a randomized trial here. It seems to
16 me that we've seen data from at least one cohort study
17 that followed a population prospectively and identified
18 a sufficient number of cases that would be needed for a
19 randomized trial. And that's even in the context of
20 passive surveillance, let alone active surveillance,
21 which would presumably identify more cases. It's not

1 clear to me whether or not the stated infeasibility of
2 the approach is attributable to their not being
3 partnerships, in-country partnerships that have been
4 established with individuals doing epidemiologic
5 research, which is certainly then a critical component
6 of successful randomized trials in other pathogens
7 where that epidemiological research and surveillance
8 has formed the basis for establishing the feasibility
9 and laying the groundwork for a subsequent randomized
10 trial. So I'm not sure that more investment needs to
11 be made in terms of building those partnerships and
12 giving a more rigorous read on the epidemiology of this
13 disease.

14 In terms of the sero-epidemiologic studies
15 that have been shown today, it seems clear, based on
16 the discussion, that there need to be more of such
17 studies. And I guess my two cents would be that those
18 studies really need to flesh out the immune response
19 profiles of the individuals who are included in those
20 studies to establish the extent to which it's the
21 neutralizing antibody responses versus other types of

1 immune responses or profiles, more complex profiles of
2 immune response that predict subsequent infection risk.
3 And in terms of the post-licensure studies, it seems
4 clear to me that those would be even more difficult to
5 conduct than the pre-licensure studies.

6 I don't see how those are more feasible to
7 conduct, and how they would provide robust efficacy
8 estimates is unclear to me. In particular, we've heard
9 mention of comparisons pre, post role out of a vaccine
10 or between clinical sites that did or did not employ a
11 vaccine. And in the context of an epidemic, that's
12 incredibly temporally varying and spatially varying.
13 Those are kind of classic cases where such contrast
14 over time and over space are fundamentally challenging
15 to make. So I really am not convinced that the post-
16 licensure estimates of vaccine efficacy would be
17 reliable.

18 As well, I feel that we've seen in other
19 disease areas situations where, once a biomarker has
20 been put forth as a reasonably likely surrogate for a
21 given vaccine and then that biomarker is used as the

1 basis of licensure for a given vaccine, it becomes then
2 even more difficult to validate that biomarker in the
3 post-licensure period. How will we -- if a vaccine is
4 licensed, how will we use the post-licensure phase four
5 data to validate the extent to which the neutralizing
6 antibody response truly predicts the magnitude of
7 protection, again, in the context of studies that are
8 even more challenging to interpret?

9 **DR. EL SAHLY:** Okay. Thank you all. Moving
10 to the second question, discussing the utility of the
11 non-human primate challenge model to assess the
12 effectiveness of chikungunya vaccines, including the
13 effectiveness endpoints: viremia, arthritis-related
14 endpoints, role of passively transferred sera, and
15 whether additional information is needed to support the
16 utility of the non-human primate model. Again, out of
17 order, we're going to go with Dr. Swamy.

18 **DR. SWAMY:** So I think that, given all the
19 things we've discussed related to feasibility --
20 whether it's an issue of feasibility, whether it's an
21 issue of finance, whether it's an issue of time -- it

1 seems to me the non-human primate model is really
2 probably one of our best avenues for getting
3 information that we want. I think particularly on
4 effectiveness endpoints, anything that we can follow
5 that is as close to the human challenge sort of
6 perspective would be best. I think the arthritis
7 related endpoints are probably going to be the most
8 likely to satisfy us from a standpoint of
9 effectiveness, the viremia, given the variation that we
10 don't necessarily know about what might be related to
11 chronic disease.

12 We're only following a challenge model in a
13 short period of time. I'm not sure that's going to
14 give us any answers there that we will be satisfied
15 with as a long-term perspective. As far as passively
16 transferred sera and so forth, I'm not sure that that's
17 going to give us anything that will be field reliable
18 as a marker of effectiveness either. I'll stop there.

19 **DR. EL SAHLY:** Thank you. Dr. Gans?

20 **DR. GANS:** Thank you. I would agree with a
21 lot of the points that were brought up during the day.

1 So I think that we've kind of entertained this. But to
2 summarize my thoughts on this, I think that we have
3 shown, at least from the data that was presented, that
4 the NHP models are actually fairly good at looking at
5 viremia and challenges to mortality and big time points
6 in the acute phase. I don't think that they actually
7 have shown any real relevance to human disease in terms
8 of arthritis related endpoints, particularly having to
9 be challenged with higher doses. So that's going to be
10 a real challenge in this model, to really understand
11 that.

12 And again, I think it's the same question with
13 the sero-epi. We haven't done the real studies in the
14 humans yet to really understand what is driving that to
15 really come up with an NHP model. There's been a few
16 Synovial studies. There have been some endpoints
17 around that. So it's hard to know exactly what's
18 happening. But that is clearly not something that has
19 been shown even in the models that are good in other
20 ways.

21 The antibody responses to the vaccines that

1 were used in the NHPs look okay. But again, we don't
2 have enough, once again, human data to know that that
3 is also something that we see in the human. And I
4 think one thing that I'm really struggling with is the
5 fact that everyone, although there is some data -- even
6 some depletion data in mice, which often doesn't
7 translate to humans -- that other components of your
8 immune system are not important. For acute disease, it
9 is clear in so many instances that humoral immunity can
10 really abort sort of viral replication, could even
11 clear it. But for a long-lasting immune response,
12 which is something that we need from a vaccine, you
13 really need other components of your immune system.
14 And humoral immunity is highly dependent on the whole
15 milieu of what happens within the context of that,
16 which I don't think has been studied.

17 So I can't say that these models are good to
18 predict any persistence of immunity. These models that
19 have been shown that are good for acute haven't been
20 challenged long-term. Obviously, if they're killed, we
21 don't get that data long-term. So I'm not convinced

1 that those models are good because, again, it goes back
2 to really having not established that immunity in
3 humans.

4 The other thing that I will just say, if
5 anything does go forward, it's going to be really
6 important to establish biobanks that we can go back to
7 and look at things after the fact because, in a lot of
8 the populations that haven't been studied -- so those
9 with immunodeficiencies -- I think that it's actually
10 going to be quite a different story. And again, in
11 these populations where there's circulation of HIV,
12 this is going to be very relevant. Children also do
13 not act like adults, especially infants.

14 **DR. EL SAHLY:** Thank you, Dr. Gans. Dr.
15 Bollinger?

16 **DR. BOLLINGER:** I thought that the non-human
17 primate data that we saw today, along with some of the
18 mouse data, was pretty compelling but obviously not
19 enough, right, to establish efficacy? So it could be
20 supportive of, perhaps, a smaller randomized controlled
21 trial in humans. I could see it being supportive and

1 then going into humans to look at other effectiveness
2 endpoints. I think the arthralgias, arthritis related
3 endpoints are going to be important, if that's what
4 we're trying to relieve the patients from. And then,
5 again, duration of immunity is going to be important,
6 as is safety. I still believe that those parameters
7 could be collected once the product has a conditional
8 approval. But it's still going to be difficult. But I
9 did think that the non-human primate data was pretty
10 compelling.

11 **DR. EL SAHLY:** Thank you. Dr. Fischer?

12 **DR. FISCHER:** So I already commented on this,
13 but I agree. I found the non-human primate data that
14 was presented to be compelling. And the question is,
15 is it enough? I think Dr. Weaver's question about do
16 we know what non-human primates are most predictive of
17 disease prevention in vaccinated humans is the most
18 important question. I think we've seen that viremia
19 can be prevented and is a good model. Again, I don't
20 know that we've seen that you could use clinical
21 endpoints. And then finally, I'm concerned about the

1 numbers. You never can do large numbers in non-human
2 primates and whether those data in and of themselves
3 would ever be enough without other supporting data,
4 which I think would be needed. Thank you.

5 **DR. EL SAHLY:** Thank you, Dr. Fischer. Mr.
6 Toubman?

7 **MR. TOUBMAN:** I'm only going to discuss the
8 first one, which I can reasonably understand. I can't
9 really understand the second one, role of passively
10 transferred sera, et cetera. With regard to
11 effectiveness endpoints, I think that as I in my
12 questioning made clear it seems that this is about
13 arthritis symptoms. And the -- I don't understand how
14 the non-human primate studies are actually useful at
15 all when these primates don't have that reaction to the
16 -- when they have a natural exposure to the virus. And
17 the only way any of the companies as reported was able
18 to illicit anything that was remotely like it was joint
19 inflammation. And that was only after very high
20 dosages.

21 So since the whole presumption of this effort

1 -- if we knew it doesn't address arthritis in humans,
2 we should terminate this entirely. It's not worth it.
3 That's the only reason to do this. So if, in the
4 animals we have, the primates, we see no indication of
5 it addressing that directly and all we have is
6 assumptions of RNA in joints and all that, I think it's
7 really problematic to use that approach.

8 **DR. EL SAHLY:** Thank you. Dr. Wharton?

9 **DR. WHARTON:** So our lack of understanding
10 about the pathogenesis of joint problems in people is
11 really a problem, and I don't think we're going to get
12 answers to that from animal models. There needs to be
13 studies done in people to get answers to that question.
14 I do think that animal data, as presented, was pretty
15 compelling regarding the ability to prevent infection.
16 I don't know that it has -- and maybe if you prevent
17 infection you prevent the joint problems. Maybe that's
18 true. But that's not going to get sorted out in the
19 animal models I don't think. But I do feel like it
20 provides very useful information regarding identifying
21 a biomarker that is reasonably likely to predict

1 protection.

2 **DR. EL SAHLY:** Thank you. Dr. Kurilla?

3 **DR. KURILLA:** Yeah. So like many of my
4 colleagues, I think the non-human primate challenge
5 model is very promising. A caveat though is, as I
6 think we heard from two different laboratories today
7 that have employed that, and I think that there is
8 probably some fundamental questions on comparability
9 but just between different laboratories using that same
10 challenge model. Most laboratories have their own set
11 of stopping rules, and that may have an impact on the
12 natural history. And I think some comparability across
13 the standardization of the animal model so that
14 different vaccines are being tested against the same
15 animal model, which will give the regulators a little
16 more confidence in looking at the data, I think is very
17 important.

18 I don't think that a single -- because of the
19 issue of this -- as was pointed out, that the arthritis
20 related endpoints are probably the more important, but
21 if that requires a higher dose -- but again, as was

1 mentioned, it may be that sterilizing immunity is in
2 fact sufficient for preventing any of the arthritis
3 that we may have to look at a combination of low dose
4 infection control in the non-human primate versus a
5 high dose to push the arthritis related effect. So it
6 may be a combination of animal model -- the way they're
7 conducted in conjunction with what should be
8 accumulating sero epidemiologic data to give us a more
9 targeted approach to what the level -- the titers that
10 we're seeing in humans can be.

11 I think, ultimately, the role of passively
12 transferred sera -- it looks so far like neutralizing
13 antisera is the key. And I think the standardization
14 around the assays of measuring that so that everybody
15 is doing it the right way is, in the end, probably
16 going to be the basis for giving us the confidence to
17 move forward.

18 **DR. EL SAHLY:** Thank you. Dr. Spearman?

19 **DR. SPEARMAN:** I'm going to echo a few of the
20 comments that have been made. I think it's a very
21 strong model for looking at immune mechanisms of

1 protection against chikungunya. It looks very
2 compelling. I think you can dissect the antibody
3 mediate protection. That can be done maybe even in
4 more detail. But it looks -- as something that would
5 also happen in humans, I think that is compelling. I
6 think the arthritis, like others have said, I'm not
7 convinced that we know what's causing that and whether
8 that's reproduced well in any of the animal models. It
9 can help generate hypotheses about what's happening in
10 humans, and that could be useful. But I don't think
11 that, as a safety endpoint, I don't think we have one
12 there for this animal model.

13 Is protection in this model reasonably likely
14 to predict vaccine effectiveness? I would say so. I
15 think it actually is a great model for looking at that.
16 There's always a gap between primates and humans.
17 There's always some unknowns. But I think this looks
18 as good as animal models of protection that you could
19 see.

20 **DR. EL SAHLY:** Thank you. I'm going to again
21 echo the data are quite compelling using the animal

1 model, with the endpoint being specifically viremia and
2 the other disturbances around the infection, not so
3 much arthritis. But I'm going to kick back the
4 arthritis issue to the issue of epidemiology. When we
5 read the epidemiology data regarding the incidence of
6 post-acute arthritis, which is three months and longer
7 -- three months being the first cutoff, I think one
8 year being the second cutoff. The data are everywhere.
9 We have from ten percent incidence of chronic symptoms
10 to -- I want to quote a study that put it in the 80s
11 percent. So the discrepancy is large.

12 Some of these studies did not have
13 confirmation of chikungunya, meaning those patients
14 with chronic arthritis could have had other diseases.
15 So even the issue of chronic arthritis, which is the
16 main thing we're trying to prevent with this vaccine,
17 in addition to sort of large outbreaks -- the
18 investment in epidemiologic prospective studies around
19 natural history of chikungunya are still needed.
20 Having said that, the model otherwise seems to
21 replicate the human data and can be used as a tool in

1 evaluating the effectiveness of chikungunya vaccine but
2 I'm not sure alone in the absence of stronger epi data.
3 Dr. Pergam?

4 **DR. PERGAM:** Yeah. It seems like we're all
5 echoing the same thoughts here. It seems as though the
6 non-human challenge model was quite good. In some
7 ways, it's kind of the best that we can get being that
8 there is no perfect animal model for the clinical
9 manifestations in human disease. I think, clearly, the
10 model showed protection from infection from viremia and
11 mortality. The arthritis, I agree, is very challenging
12 to assess. I sort of like the idea of the dual sort of
13 levels where you have a low-level exposure and a high-
14 level exposure for the two different endpoints. But
15 I'm not sure that, if we really believe that viremia is
16 the driving force and that the primary infection is
17 related to viremia, if we think that that's the cause
18 of arthritis, I'm not sure we're going to get better
19 than what we have. So I feel like it's about as good
20 as we're going to get. I'm not sure there's much we
21 can do to improve upon what's already been done.

1 I think the role of passively transferred sera
2 from vaccinated humans -- again, I think it's a sort of
3 similar process. I think it looked from -- sort of
4 what had been presented is this looks as though it
5 would be potentially a method to predict vaccine
6 effectiveness. I think it will be important as we move
7 forward. I'm not sure that I was totally convinced of
8 the data I saw.

9 And then, additionally, going back to what Dr.
10 Gans said, I'm sort of curious about, in the non-human
11 primate challenge model, are there other aspects of the
12 immune response that they can evaluate that would at
13 least be similar and reflective beyond antibody
14 responses alone to see if any are potentially
15 predictive for associations of importance? Is there
16 some other aspects that we can look at in terms of
17 controlling chikungunya that might be important from
18 the vaccine responses?

19 **DR. EL SAHLY:** Thank you, Dr. Pergam. Dr.
20 Meissner?

21 **DR. MEISSNER:** I really don't have anything

1 novel to add to what's been said. I think that Dr.
2 Fischer said it, and I agree most succinctly, that the
3 animal data are terrific and very helpful. But is that
4 a sufficient basis on which to proceed in humans
5 without an efficacy trial?

6 **DR. EL SAHLY:** Thank you. Dr. Janes?

7 **DR. JANES:** I guess I have a slightly more
8 maybe nuanced view on the non-human primate data. I
9 guess I would suggest that there are a number of
10 attributes of the way that the non-human primate
11 studies are being done that could potentially be
12 tweaked to more precisely characterize the potential
13 efficacy of these vaccines in humans. It's hard to
14 know without those attributes being changed whether or
15 not they matter. But it strikes me that, as mentioned
16 in a summary this afternoon, that in addition to the
17 non-human primate models not recapitulating, not
18 capturing the acute and chronic arthritis but also the
19 challenge -- the dose of the challenge being pretty
20 much uniformly a single high dose challenge as opposed
21 to repeated exposures in a human population with a

1 lower dose exposure given via a bite from an infected
2 mosquito.

3 So it raises in my mind the question as to
4 whether or not the results in a non-human primate model
5 would be different if there were lower dose challenges
6 and challenges given via different route instead of
7 intradermal exposure -- an exposure more mimicking
8 natural exposure in humans. Hard to know given that
9 those studies are fewer than the studies that we heard
10 today. As well, it seemed that the studies have
11 largely used challenge with homologous virus as opposed
12 to heterologous virus, which would be what humans see
13 in a natural setting. Hard to know whether or not that
14 matters given that the studies have not, generally
15 speaking, used heterologous challenge.

16 And as well the studies having used pooled
17 human sera from vaccinated individuals as opposed to --
18 with the exception, I think, of a study that looked at
19 two individual subjects in a vaccinated population,
20 there would obviously be heterogeneity in the immune
21 responses that are induced by the vaccine. So to what

1 extent does that heterogeneity and immunogenicity
2 result in heterogeneity and protection from infection
3 in the challenge model? So it seems to me that it's,
4 particularly if the non-human primate challenge data
5 are going to be used to critically inform licensure as
6 they would under an animal rule, it seems important to
7 me that these aspects of how the studies are done be
8 investigated a bit more in depth to determine the
9 extent to which they ought to be modified or studied in
10 order to determine whether or not tweaking those design
11 parameters would yield different results.

12 And I'll mention that, in a non-human primate
13 challenge study in HIV studying protection from SIV
14 challenge, repeated low dose challenge studies have
15 proven to be exceptionally helpful and informative and
16 much more closely mimicking human exposure to HIV. So
17 I would suggest considering those here.

18 **DR. EL SAHLY:** Thank you. Any parting
19 remarks, Dr. Gruber, Dr. Fink?

20 **DR. GRUBER:** I was sort of silently sighing
21 when I heard the discussions. But in so many ways, it

1 really reflected internal discussions that we had
2 within the Office of Vaccines. And we also had
3 pertinent discussion, of course, with regulated
4 industry. I think, however, that this was a good
5 discussion. There have been really lots of different
6 perspective expressed.

7 I was somewhat encouraged regarding the
8 remarks made in particular regarding the non-human
9 primate challenge model. I think we will have further
10 discussions in terms of what data we need. Do we need
11 additional data? Would the models need to be tweaked
12 as was just suggested? But I think -- so in general,
13 at least in my mind, from my perspective -- and I
14 didn't have discussions with my colleagues.

15 But of course, I have a certain perspective
16 based on the data that I have seen. And I think it has
17 been solidified by the discussions that have taken
18 place this afternoon. So I have to say I want to thank
19 the committee. I think it was a helpful discussion.
20 And I think perhaps you all sort of -- I think
21 sometimes, "Welcome to our world," when we have these.

1 Of course, everybody likes the idea of
2 randomized controlled clinical pre-licensure study.
3 But we also have to be realistic, especially for these
4 emerging infectious disease vaccines. There are
5 different challenges, and we have to carefully think
6 through and see what else is within the toolbox. Is
7 the RCT really the only way to demonstrate
8 effectiveness of a product? And these are discussions
9 that we have ongoing right now. There's a big
10 initiative across the Agency, across the centers
11 discussing the topic of real-world evidence and how
12 they can help demonstrating the effectiveness of
13 therapeutics, as well as preventative vaccines. So I
14 think we have to look at all these different aspects as
15 we continue our discussions with regulated industry on
16 a path forward to demonstrate the effectiveness of
17 these products.

18 So these would be my comments. Lastly, I
19 really want to again thank you to all of you. I know
20 this was a challenging very difficult discussion to
21 have. I want to know if maybe one of my colleagues

1 want to add to this? Have additional comments to make?
2 Let me turn around. No, they don't really want to say
3 anything today. Okay. Well, thank you very much,
4 again.

5 **DR. EL SAHLY:** Meeting is adjourned.

6

7 **[MEETING ADJOURNED FOR THE DAY]**