

CDC Ebola Response Oral History Project

The Reminiscences of

Kevin M. De Cock, H. Clifford Lane,

Frank J. Mahoney, and Oliver W. Morgan

David J. Sencer CDC Museum

Centers for Disease Control and Prevention

2016

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Interviewed by Samuel Robson
July 14th, 2016
Phone call
Interview 1 of 1

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Q: The date is Thursday, July 14th, 2016. This is Sam Robson, director of the CDC [Centers for Disease Control and Prevention] Ebola Response Oral History Project. Today I'm joined by people around the world to discuss the collaboration between CDC and NIH [National Institutes of Health] during the West African Ebola epidemic of 2014 to 2016. With me here in Atlanta is Dr. Oliver Morgan, advisor to the World Health Organization on behalf of CDC. During the epidemic, Oliver served as CDC's lead in Sierra Leone before coming back to CDC headquarters in Atlanta and overseeing the response as a whole. Calling in from Geneva is Dr. Frank Mahoney, who is currently seconded to the International Federation of the Red Cross while working with CDC's Global Immunization Division. And calling from Kenya is Dr. Kevin De Cock, country director for CDC's office in the Republic of Kenya. During the response, Frank and Kevin rotated as leads in Liberia and also served in important capacities later in Guinea and in Nigeria. So that's wonderful. And eventually joining us will be Dr. Cliff Lane of NIH who oversaw NIH's scientific efforts during the 2014-16 Ebola response. So thank you all, again, for being here. Frank, I think maybe we'll start with you because I know you have limited time before you have to take off. Do you have any specific memories of collaborating with NIH and with Cliff or Kevin that surface when you think about the ZMapp RCT [randomized controlled trial]?

Mahoney: Well, I actually had worked with Cliff and members of his team in Indonesia. It was probably back in 2009 to 2011. There was some interest in those years to set up a clinical trial network, and I was working as the CDC country director at that time, so I helped facilitate Cliff's establishment of the clinical trial network which I think is running to this day in Indonesia. I knew him and I knew members of the team that were coming out. He was coming out and doing some work on I think HIV [human immunodeficiency virus] and emerging diseases, and so I met Libby [Elizabeth] Higgs and Laura [A.] McNay on his team. It was great to work with them again when we met again in [Liberia], and the fact that we had worked together in the past really helped a lot. I think the role that I played with him on setting up the clinical trial network was similar actually to how we worked in Indonesia. It was mostly facilitative, helping him, marshaling through the politics of Liberia and introducing him to the EOC [emergency operations center], attending some of the scientific meetings with him, and watching him and the team set up their operation as they set up the process for doing the clinical trial. I do remember talking to him about it, and I think at the time we were discussing how quickly he would be able to get the trial running and whether there would be a race against getting to zero and his ability to actually get an efficacy input. In other words, I was fairly certain by the time they were ready to start the trial that we would be almost down to zero number of cases for Liberia. So their ability to actually demonstrate efficacy of the vaccine would be diminished because the outbreak would be almost over, and I think essentially it was over by the time he got started.

Q: Frank, can you also tell me how you first got involved in helping coordinate these clinical trials?

Mahoney: It's hard to remember. I can't remember exactly the first contact I had with Cliff on this. I know we had some email dialog. I think throughout we were in touch about setting up a trial, the timeline, whether there would be anything ready. I think early on I had had some email correspondence, and I think there were some scientists from Liberia going to meetings in Geneva. I think Stephen—I think his last name was Kennedy—was going to meetings where he saw Cliff at the planning meetings in Geneva. And then I think when he [Cliff] first came out, I helped facilitate his visit. We helped find him a place to set up and meet with the ambassador and set up his operation on the embassy grounds.

Q: You mentioned helping Cliff and NIH kind of marshal through the politics in Liberia. What did that mean?

Mahoney: Well, I think it was fairly complex. It was a randomized trial. A lot of people just wanted to go out and vaccinate, and so we had to help people understand the importance of doing a clinical trial, a randomized controlled trial. I think some of the partners were discussing whether or not they should just do quote-unquote “compassionate use” and just use the vaccine, and Cliff, as the good scientist he is, was very firm that that's not the way NIH works and that's not the way you do clinical trials

in a setting like this. There were people second guessing whether or not we should be doing a randomized trial in a setting like this.

Q: Right. I don't know if Cliff is on the line right now?

Lane: I just joined, thanks.

Q: Great, thanks. Cliff, can you introduce yourself quickly?

Lane: Hi. Cliff Lane, clinical director, NIAID [National Institute of Allergy and Infectious Diseases].

Q: Can you briefly describe the ZMapp RCT for us?

Lane: Sure. The ZMapp randomized control trial, also referred to as the Medical Countermeasure Trial, also referred to as PREVAIL [Partnership for Research on Ebola Virus in Liberia] II, was a generically designed study to look at a comparison of whatever the standard of care was at an ETU compared to that standard of care plus the ZMapp intervention.

Q: Thank you, Cliff. We were just speaking with Frank and starting to dig into the issue about some of the ethical concerns that came up with this ZMapp RCT, that some partners—

Morgan: Sorry, Sam—hi, Cliff, this is Oliver. I was wondering if we could actually just go back to the start. Kevin was going to talk a little bit about how the collaboration started, because there were several components to NIH's—the ZMapp was one but there were others. Maybe we can go back to the beginning and map it out chronologically. Does that work for everybody?

De Cock: Sure. This is Kevin, maybe I could start. I think the consideration for collaboration goes back to July of 2014. I arrived in Liberia on the 16th of July and a week to ten days later we were dealing with the—well, we dealt with a lot, but another issue we were dealing with was infections in the staff at Samaritan's Purse, particularly the American physician Kent Brantly and Nancy Writebol, a nurse. The lab work for the support for the response which CDC helped coordinate was actually being implemented by Liberian technicians and scientists, but critically supported by staff from NIH and USAMRIID [United States Army Medical Research Institute of Infectious Diseases], particularly Lisa [E.] Hensley who was a research scientist. She was really my main point of contact, and she was herself doing and supporting lab work out in the Liberia Institute for Biomedical Research near the airport some fifty kilometers outside of Monrovia. When these two individuals got sick, there were many, many issues immediately raised, like what care can be provided for expatriates who get infected, the issue of medical evacuation, and the issue of any further medical support. Lisa actually was a researcher on hemorrhagic fevers and—Cliff may correct me if I'm wrong, but was actually supervised by Cliff. The whole issue of access to unlicensed medicines came up, and in

fact through various channels, ZMapp was provided to those two individuals, as I believe it later was in the United States to expatriate staff evacuated. That was sort of some initial collaborations or contact with NIH.

The second somewhat analogous situation was when President [Ellen] Johnson Sirleaf wrote to President [Barack H.] Obama asking for access to experimental medicines for Liberian physicians infected in the course of their work, and we got involved in those discussions. Then, just before I left, and actually I think it was following that correspondence from President Johnson Sirleaf to President Obama, that I spoke with the minister of health, Dr. [Walter T.] Gwenigale, and the chief medical officer, Dr. [Bernice Dahn], to say listen, maybe you should ask for assistance for research collaboration or evaluation of biomedical interventions in the context of this very severe epidemic. I knew Cliff, and I got Dr. Dahn and Dr. Gwenigale to sign off on a letter, to write a letter, that was transmitted to the NIH. So I think those were the initial contacts.

There was then a somewhat slow response. Not Cliff's fault by any means, but sort of the official machinery, the diplomatic health machinery through HHS [United States Department of Health and Human Services] and back to Liberia was somewhat nonspecific and a little bureaucratic initially. I think I remember calling Cliff to say listen, if we want to make this work, we're going to have to be much more specific in the assistance that can be provided. This was all in the early days. This was all July, August, maybe into September of 2014. Let me leave it there. I think those were the initial contacts made.

Lane: I can pick up a piece right there from Kevin. Nice to hear your voice, Kevin, and Frank and Oliver. So when Kevin called me about this, my concern was obviously this was not going to be easy. We were going to need to be sure that we had clear support and buy-in from the top down, and that's why it was so important that Kevin worked with Minister Gwenigale, and then he actually sent a letter that went to Secretary [Sylvia M.] Burwell asking for that type of assistance in putting in a research program. As Kevin said, I think the response took a while to get back. I think it probably went back something official like October 2nd or something, and then that was my imprimatur from HHS to then go over. I was over there right after that, basically I think almost two days after that letter, October 4th, which is where Frank was then the country lead. Frank was phenomenal in facilitating all the right discussions and planning of who to speak with, who the communities were. I remember so vividly he introducing me to Mosoka [P.] Fallah, and we went to West Point and met with some of the trackers to hear about some of the perceptions regarding research. I think I should stop there. I know Frank was talking right when I came on probably about that period of time.

Q: Frank, do you have anything to add about those discussions that you helped facilitate?

Mahoney: No. I think from that time on I was impressed by Cliff, the team that they brought in, and how quickly they were able to set up there. It was quite amazing, their operation and how they engaged in establishing procedures for people to enroll in the study and how quality the whole operation was. It was quite impressive to see it so

quickly established. I think we enjoyed—I think having previously worked with Cliff and Laura and the team, it really helped a lot. We had a good working relationship.

Lane: Just to clarify, the discussions that we had with the Ministry [of Health and Social Welfare] and other stakeholders led us to identify an immediate need to try to put a vaccine trial in place. So that work that Frank is reflecting on really was the randomized control trial of the VSV [recombinant vesicular stomatitis virus] vaccine versus the ChAd3 [chimpanzee adenovirus 3 vaccine] versus a placebo. That was where the initial work took place. Again, I heard Frank mention as I came on, it was interesting to talk to the different stakeholders because while in some instances one could make the cogent argument about the scientific approach that would lead to the best information the quickest, which in my mind then would extend the greatest public health benefit to the greatest number of people as quickly as possible, there were some stakeholders who just absolutely rejected the notion that you could do a randomized control trial, much less a placebo randomized control trial. So that did take a bit of discussion, but to my I guess happiness, once those arguments were put out there, most rational people could understand that it wasn't that this was like some scientific thing we were doing to publish papers, but it really was the approach to get the answers that we were trying to get to at that time.

Mahoney: I recall it wasn't a decision they took lightly as well. They had their whole medical society, big meetings, excluding us in those meetings where they were discussing these issues. It wasn't like a few researchers making a decision to do this. It was quite

impressive how they had a very deliberate debate and discussion and came up with an agreement or decision to participate.

De Cock: Just to echo Frank's earlier comments, I think the collaboration between CDC and NIH was very good. I mean this was an NIH-run trial with partners, so our role was really supportive more than anything else, but the fact that we were on the ground fulltime I think helped the important contact that we'd made. Like Frank, Cliff and I have known each other a long time, mainly from the AIDS [acquired immune deficiency syndrome] world, HIV/AIDS world. I'd known Libby Higgs as well and also interacted with the statistician, Jim [James D.] Neaton. So just knowing everybody was very helpful. Also the Liberians took all this very seriously because it was discussed with the president at the high-level Ebola policy group that had been formed. I remember I think it must've been November/December 2014, meeting with the president and other high-level officials and selected ambassadors and so on, and saying that this was extremely important to do. Cliff is of course right to discuss separately the vaccine trial from the ZMapp trial. These were two separate trials. Then the only other event that I remember from that time was in early December 2014. I went over to Sierra Leone at the request of the government of Sierra Leone, somewhat organized by the US Embassy there. Met with Oliver, who was the team lead in Sierra Leone, and by this time cases in Monrovia and Liberia had really fallen to very, very low levels, less than ten per day nationally. It was pretty clear that the very ambitious vaccine trial, which required some twenty-eight thousand participants and a reasonable incidence to be able to show any definitive results, it was clear that that was not going to be possible. But Freetown at that time was having a

very brisk epidemic. Our estimate I think was they probably were having at least one hundred cases a day if I remember the discussions with Oliver, and Oliver and I discussed the importance of the ZMapp trial in Freetown or trying to extend it to there. It was just critically important. I think also when it comes to the ethical discussions, I think it's useful to discuss separately the ZMapp from the vaccine trial, but fundamental to both of course was the consideration or the opinion that there was equipoise in the two arms of the trial, the placebo and the active product, because one really didn't know whether these products were effective or not.

Lane: I can maybe do a segue that would get us then over to ZMapp and Sierra Leone if that sounds reasonable.

Q: Sounds great.

Lane: As Kevin was saying, we launched the vaccine trial initially and in fact, as those cases and the incidence went down, we pivoted that research to then become a program to focus on Ebola survivors to be able to try to better understand the longer-term complications as well as perhaps get a bit more information on the nature of protective immunity. But as those things are happening, there's all the other things that were happening and one of the things that was really quite, I have to say, important in my thinking was when we received one of the Dallas nurses to our treatment unit. She had become infected in the US, as had been the case to that point to I think everyone who had been medevacked from West Africa. These two nurses in Dallas, they were given

anything that anyone could get their hands on pretty much. When we saw the patient here, the only thing that was clear to us at the time was that there probably was toxicity from some of the things that had been provided, and it was I think so clear at that moment from a clinical research perspective that we knew so little about these agents in humans—they had been in a variety of animal models—that if we were ever going to sort through it, we had to do it with a study designed that allowed one to make that distinction not only of efficacy but also of safety. And from there we worked with really on the US side interagency as well as multiple pharmaceutical companies, and I remember because it was on Veteran's Day 2014 we held a meeting here at NIH. That's a good day to get people, as you can imagine, because it's a federal holiday. We had the companies come in and present to this group with representatives from CDC, DoD [US Department of Defense], NIH, and five or six companies, to present us their latest data with the idea that we were going to study in this medical countermeasure trial those most promising agents. We came out of that with a clear consensus that ZMapp was the most promising agent, that that would then go into the study. That protocol became active early in 2015. In fact, the first person enrolled was the last person—at least thus far, knock on wood—evacuated to us with Ebola, a case from Sierra Leone that Oliver is aware of. That was the first enrollee. The next few enrollees were actually in Liberia initially, at the Monrovia Medical Unit. From there, as Kevin was saying, the number of cases in Liberia had gotten so low that we were looking to where we might extend the study in the region. Just coincidentally, there had been someone in Sierra Leone that somehow had gotten a dose of ZMapp. It was certainly the preliminary data that you needed more than one dose, and there had been a reach-out to us from CDC and from the Ministry as well as the [US]

Embassy, could we get additional doses of ZMapp over? That began discussion about then extending the study. I think that would be a good point for Oliver to pick up.

Morgan: Thanks, Cliff. The situation in Sierra Leone was quite interesting. I would say similar to how Kevin described, the Sierra Leone medical and research community were really interested in engaging in research but in a very responsible way. The story of ZMapp in Sierra Leone is quite interesting in that in December 2014, the most prominent physician in Sierra Leone, called Dr. [Victor] Willoughby, was diagnosed with Ebola virus. He was the physician to the president and all of the—I guess the rich Sierra Leonean society. When he was diagnosed with Ebola, Austin Demby, who works for the Office of Global Affairs up in HHS, was in-country. Austin knew Dr. Willoughby from his childhood because Austin is a Sierra Leonean and grew up in Sierra Leone. Austin reached out to the ZMapp company in Canada and actually got somebody, amazingly, to hand-carry some doses of ZMabb. Because at the time there was no ZMapp left in the world, there was only the ZMabb product which, Cliff, you can correct me if I'm wrong, but I believe is a laboratory product, not really with the intention of being used outside of a lab setting.

Lane: Yes, it's two of the three antibodies in ZMapp, so the two antibodies that came from Public Health Agency of Canada.

Morgan: Okay, thanks for the clarification. So Austin really quite extraordinarily managed to navigate all sorts of hurdles to get someone to hand-carry the ZMabb over.

Unfortunately, as they were sorting it out, Dr. Willoughby passed away. But then they were left with this dose, I think it was one or two doses of ZMabb in the country. Then when—I believe it was a Bosnian healthcare worker—got infected and chose to stay in Sierra Leone rather than be expatriated to somewhere else for his medical care, I think that's when the discussion about providing the ZMabb and additional doses of ZMapp occurred. I had many conversations late into the night with the NIH team in Liberia about bringing over one or two doses. That really paved the way in Sierra Leone for the ZMapp trial to be discussed with the Ministry of Health and for them to be enthusiastic and receptive about it. Maybe that would be a good point, Cliff, for me to hand back to you to describe how things got set up in Sierra Leone and then maybe we can come back to just a couple of anecdotes about the first patient to be enrolled into the trial, because I recall that was a particularly exciting moment.

Lane: That's good. It was pretty much like how we started in Liberia, with myself and one other person. We traveled to Freetown and Oliver was there, CDC was there. They took us to meet all the right people from the government and the other stakeholders as well. It was interesting that while many of the individuals we spoke with and went through the rationale for doing a randomized control trial would understand quite well why we thought that was the right approach, there were other groups—I would say MSF [Médecins Sans Frontières] prominent among them—who just rejected that idea. That actually wasn't so much a constraint for us in Sierra Leone. It did actually become a constraint as the trial moved into Guinea. But I think it was such a great example of collaboration between the two health agencies, CDC, NIH. Great help from Ambassador

[John] Hoover and the team at the embassy. Again, I marvel really of Kevin, Frank and Oliver, how all three of you were able to get me to the right places in a very short period of time. Most of those initial visits were just two days, two and a half days maybe, but we managed to get to the right places, do presentations to the right groups. There were obviously multiple, multiple follow-up meetings but it was pretty clear after that first visit that we did have a path forward. We met with the regulatory agency and I can remember large volumes of cash that we had to take to the copying place to get the right number of copies of regulatory submissions. Then we looked for a dedicated team of people from NIH and that same extended family that Kevin mentioned earlier, people who had done this type of work in the past who were committed to doing this type of work, and we set up shop in what had been I think a small business center at the hotel. The CDC had a great place at the Radisson [Blu Mammy Yoko Hotel] called the Cave that was there 24/7 [twenty-four hours a day, seven days a week] to provide whatever you needed in terms of faxes or printing, which we took advantage of. The team [was] then hired, through the amazing help that we got through Oliver with the CDC Foundation. I don't think we could've moved as quickly as we did in Sierra Leone because we did not have the same footprint in Sierra Leone that we did in Liberia. We couldn't have moved anywhere near as quickly as we did without that help that came through Oliver and the CDC Foundation. So back over to Oliver to talk about the first patient.

Morgan: Thanks, Cliff. I think we all found this a really enjoyable and exciting collaboration. I just wanted to tell the anecdotes about the first patient because at least from my perspective it was a fascinating experience. We had a notification early one

morning of an individual, a US citizen, who was working with Partners in Health, who had been admitted to the UK [United Kingdom] military ETU which had become designated as the place for foreign medical workers to be isolated and cared for when they became infected. And very quickly, because it was known that there was some ZMapp in country, there was talk about using ZMapp for this individual. I got on the phone with the UK military medical unit and started to discuss this with them. I think I called Cliff at the early hours in the morning. I probably got you out of bed at about two o'clock in the morning, Cliff, and we started discussing about enrolling this individual into the ZMapp trial. Throughout the course of the morning, we had the right discussions. We actually even pulled the chief medical officer out of a meeting with the president of Sierra Leone to get his approval to use ZMapp in country because this is not a licensed product. And everything seemed to be going pretty well until we then got a response from the UK leadership saying that they were not prepared to participate in the randomization of this individual into the ZMapp trial but they were quite happy to provide the ZMapp on compassionate grounds only. We then expanded our conversation to include Ambassador Hoover, who also had a very distinct position and viewpoint, and he articulated that very clearly in a telephone conversation that we had with—Cliff, you might have to remind me, it was yourself and myself and some other very senior individuals in HHS. Do you remember who else was on that call?

Lane: I can't. I'm guessing Dr. [Anthony S.] Fauci was probably on that call but I honestly don't remember for sure.

Morgan: It was a conversation that went all the way up to the HHS secretary about how we should proceed. Ambassador Hoover was very clear that in his view, his job was to do the very utmost for all American citizens in Sierra Leone in his role as ambassador and his view was that the individual should receive ZMapp regardless and not on compassionate use and not be randomized. And as I mentioned, the UK position was that they would only give it on the compassionate grounds or for compassionate use, and on their side the issue also escalated all the way up to the chief of the head of the UK military medicine and also up through their ministry of health. I'm not quite sure how high it got, but these were discussions that happened really within a matter of hours, and maybe I'll hand it back to Cliff to maybe reflect on some of those conversations and maybe tell the story about what happened in the end.

Lane: Sure. So it was obviously a very difficult situation for everybody. And just to clarify, we're talking about the very first patient enrolled in the study, not the first patient to be enrolled in Sierra Leone. This was Patient One. The discussions were that there really wasn't, from I think our side at NIH, there wasn't anything that compelled this person to get open label drug while at the same time we were doing a randomized control trial. Usually the paradigm is, well, if someone is not eligible for a study and you think your investigational drug might be of benefit, then you could do what's called an emergency IND [investigational new drug] or single-patient exemption. There were none of those factors here. The person was clearly eligible for the study, there was a way to randomize, and we felt that it really would be unethical to feel that this person, solely for the fact that they were an American, would be treated differently than anyone else who

got infected that same day in Sierra Leone or Liberia. So it was very difficult and as Oliver mentioned, a lot of differing views, and at the end the decision was that if he was willing, we would enroll him in the study but that would not be able to take place until he had been medevacked back to the US. He was actually coming to the NIH clinical center, the next step for the patient and as he came here, he was able to consent. His case has been published. He was quite ill. He was, as Oliver mentioned, with Partners in Health. We had discussions not only with the patient, with the family, even with Paul [E.] Farmer who had been obviously one of the two founders of Partners in Health, and I think on that side, on the NIH side, on the Partners in Health, the family, the patient all understood what we were talking about, and was then enrolled in the study, as one can see from the publication that will come out shortly on the trial—hopefully knock on wood that it will. He was randomized to the control arm and he survived with a fairly rocky hospital course. And what was quite interesting, I have to say just as a little bit of a side note on this, is that individual later on had a chance to go back to West Africa and see—I think again from an entirely different perspective—the importance of doing things in a rigorous way so that when one comes to answers, that then can help larger numbers of individuals. And it, I think for him, crystallized actually. I don't think he fully appreciated how important his role had been, and in fact from our side we had been getting a lot of criticism, I have to say, and it doesn't really matter where it was coming from but it was from people who were quite influential that, well, the Americans talk about randomized control trials but when it comes to their own people, they just give them the investigational drugs. And then here was a very clear example of where that was not the case because I think that what we did was the right way to proceed. But it was really a

very interesting and challenging set of decisions and actions downstream from those decisions.

De Cock: If I could just add on, which I think will probably sort of close the story, I'm on the program committee for the annual retrovirus conference, the Conference on Retroviruses and Opportunistic Infections, known as CROI, a very influential HIV conference. But in 2015, there was a special session on Ebola. Nothing to do with HIV, but because of the severity of the epidemic and the interest of the audience, a special session was held, an evening session with a couple of talks, one of which was given by Cliff. Very successful, well-received session. In 2016, there was another special session but this time with data including from some of the studies Cliff has talked about like the NIH-sponsored study of survivors. There was also a presentation on the results of the ZMapp controlled trial. Cliff, do you want to give the results?

Lane: Sure. The study was presented by Dr. Richard [T.] Davey, who was the global PI [principal investigator] for the study. Again, fortunately the number of cases had gone down. There had been no cases for I think about certainly over twenty-one days in January, so at that point, January 2016, the study was closed. The data were analyzed and while it did not hit the conventional statistical significant p-value of .05, it certainly had a p-value of .09 showing a survival benefit to individuals who received ZMapp compared to individuals who were randomized to the optimized standard of care. It was clear that that benefit, if it was there, was seen at all stages of illness as defined by viral load at the time of study entry. And I think based upon those data, coupled with the other data that

are available from the pre-clinical trials, so we're hopeful that this will then become hopefully a licensed intervention for patients with Ebola virus disease.

De Cock: I chaired that session. Having listened to the results, and they're available on the web, on the CROI website as a webcast. I mean certainly I think the results, because of inadequate statistical power, statistical significance was not reached. They're very suggestive. They certainly suggest a survival benefit in ZMapp recipients and I think what's important is that if anything, heaven forbid, happened like this again, I think there would no longer be equipoise in the way that we look at ZMapp. In other words, I think most reasonable people would interpret available information is suggesting that ZMapp is beneficial. But I think what the whole discussion does raise is the awkward balance between on the one hand equipoise—you know, if you don't know whether a medicine is effective or indeed whether they're safe, without a randomized control trial, there's no way of knowing what the right course of action is—and that has to be balanced with compassionate access if that is deemed the right thing to do. How you balance those out can be very difficult, and of course the number of cases is a relevant consideration because you can't do a trial if you don't have enough incidence. It's sort of relevant to another medicine that hit the headlines, the product GS-5734 made by GSK [GlaxoSmithKline plc] which was used in the famous case of the Scottish nurse, who has relapsed a couple of times, and who did receive this product and that was written up in *The Lancet*, but again, no data other than from experimental animals. So many interesting considerations at different stages of the whole story. Cliff, any comments on that?

Lane: No. I would just add I completely agree with Kevin that certainly from my perspective we are not at equipoise for ZMapp and in fact, Mapp Bio [Biopharmaceutical], the pharmaceutical company with that product in their portfolio, has not been in contact with each of the three ministries of health in the three outbreak countries to look at the ways in which ZMapp would be provided. Again, we're providing support up to the point that they're able to take that over with some work with CDC. But if there were a new case of Ebola today, we would do everything we could to get ZMapp for that participant. So in that regard from my perspective, that study was very successful in moving us from not knowing to having a fair degree of certainty that this is something that would add benefit and I think, as I said, will become the treatment if at all possible for the next case.

Morgan: I'd just like to reflect a little bit on that very end stage, as Kevin was mentioning, the issue of equipoise and whether there was still equipoise towards the end. When I was here working as the incident manager at CDC and we were really seeing the last chain of transmission in Guinea with this handful of cases at the end of 2015, it was an enormous amount of pressure especially from Dr. Frieden to see if ZMapp could be used. Also a lot of pressure from MSF for all cases in Guinea, and we did in a couple of instances make a clear case for compassionate use, we used on compassionate grounds for infants. I think it's really just an interesting and probably nice conclusion to the story that the last individual—correct me if I'm wrong here Cliff—I believe who received ZMapp was baby Nubia, who was the only baby to have been born to an Ebola-positive mother to have survived. I think everybody really felt that it was clearly the right thing to

do. I'm sure Cliff will remember, we had many conversations and, again, at a very high level. Individuals were engaging from FDA [Food and Drug Administration], from HHS, and really all the way to the very, very end of the trial.

Cliff: Yes. Just to put a little additional perspective on that, because there's a very sad and tragic piece to it, that again, the baby and the mother were at an Ebola treatment unit that was managed by MSF and MSF would not engage in the randomized control trial and so the mother, who was eligible for study, I think died—was not enrolled in the study. The baby, who would not have been eligible as an infant, did receive the drug and as Oliver mentioned, survived. I have to say one of my regrets from the study was that we were not able to engage MSF to be a partner despite the strong support from Dr. Sekoba [Keita] and the Ministry of Health in Guinea to do that and support from many of the other investigators. I think it reflects some of the real challenges in doing research in these settings in that there are many, many people as we talked about earlier from the start for us in Liberia that you need to engage if you're going to try to move something like this and move it successfully, and there are successes as well as failures in what we did.

Q: I want to clarify a couple of points if that's okay. Did MSF refuse to participate in the randomized control trial because it was their position that everyone should be given ZMapp?

Lane: Yes. Their position was everyone should be treated the same. Now, towards the end they were trying to negotiate that, well, maybe we could randomize people with high CTs, people with low viral loads, but that we would give open label to people with higher viral loads or low CTs, which to us didn't make sense. There were statements frequently thrown out that this group had 100% mortality although really when you looked at providing some degree of support, you couldn't tell what that mortality was and, again, I think the figures from the randomized control trial show you did not have 100% mortality by any stretch of the imagination in the control arm. So they did not want to participate in that type of study. Multiple discussions took place with them, with us, with CDC, actually with the department, with ASPR [the Office of the Assistant Secretary for Preparedness and Response], with FDA, with the French research agency INSERM [National Institute of Health and Medical Research]; that's a pretty strong position that they held centrally and then that fed out to their units in the field.

Q: My follow-up question then is I'm not sure to what degree ZMapp was scarce. Had everyone agreed that all people diagnosed with Ebola should receive ZMapp, would there have been enough of this treatment to go around?

Lane: At the time the study was initiated there was.

Q: Thank you for that. I think we're going to try and move toward the larger significance of all of this. I have a question about what ZMapp and beyond ZMapp, the vaccine and

the survivor trials, all of CDC and NIH's scientific work in West Africa means for the future of science conducted in emergency situations.

Mahoney: I have to check out. I have someone else to meet and I've got to ride my bike across town.

Q: Thank you, Frank. I really appreciate you coming in.

De Cock: After this last question I'm going to have to sign off as well. I've got another meeting.

Q: I think this is a good conclusion actually.

De Cock: Well, let me go first. I think the whole experience shows it's very difficult to conduct science under these very stressful, adverse conditions. Adverse because of the sheer severity of the epidemic and the environment. I mean it's not a coincidence, as we discussed previously, that the epidemic was so severe in these particular countries because they were so weak—the infrastructure is so poor, there's so few people, technical and professional people to work with. It was just an extraordinarily and historically unique situation. Having said all of that, I think science is required in these very settings to answer these critical questions and I think in retrospect I think we did miss an opportunity. I think we should've gotten engaged, and this is not a criticism of any of us or any particular organization. It's really a comment on the world's capacity to deal with

these situations. I think we should've gotten involved from a scientific basis earlier because we missed opportunities and there are still unanswered questions that we now cannot answer: the relative efficacy of these vaccines. We do have some data from Guinea but we don't have—and Cliff can comment better—we don't have all of the data we need. We don't have data on one of the vaccines nor indeed on other drugs, and it's because we were unable to marshal all the resources necessary when incidence was high. Let me stop there. There's other aspects, I think there's other research questions as well, more on epidemiology, on clinical manifestations, on very important questions like does asymptomatic infection occur and if so, how frequently, which are important and could've been answered with more focused research. But understandably but regrettably, all of the attention went to the epidemic response.

Q: Kevin, thank you so much for participating in this. I love having your perspectives and your experience recorded. So thank you.

Lane: I might just add on to what Kevin said, hopefully, Kevin, while you're still here, is that I agree completely with that. In point of fact, there were incredible research opportunities that we as a global community failed to capitalize on, failed to take advantage of, failed to generate the knowledge that could've been so valuable for us dealing with Ebola virus infection in the future, and we have to do a better job of this going forward. We have to have systems whereby one can objectively look at what opportunities for research are there in terms of products, in terms of questions, and then decide what makes the most sense in terms of experimental design to get the answers to

those questions and then working together to get those done. In a way, it was less in my mind a matter of actual resources as it was a lack of international cooperation in identifying the most critical questions and how to address them. There's a lot of lessons learned exercises. IOM [International Organization for Migration] is looking at the equality of the research response, and I hope that we can take from that ways in which if we get in this type of situation again, we have a more coherent and effective response internationally.

Morgan: I would just like to add on reflection of what we managed to achieve jointly. Although I certainly agree that we could've done more and hopefully in future events we will do more, I do think we did accomplish an extraordinary amount. I think as we've all discussed, it was based on this great partnership between CDC and NIH, and I think both of us as agencies and individuals, I think we would probably do a better job next time. I think we'll probably get out of the starting box faster. I think the ongoing partnership is an important one. I think we achieved more probably than almost any other group. I think the ZMapp trials, the only kind of real RCT that was actually implemented—but I think, as Cliff said, lots of lessons learned exercises hopefully going to guide us with a better response on the science side, and getting that balance between response and science I think is always going to be a challenge for us.

De Cock: I'm going to have to sign off, so great to talk with you. Thanks Sam, Oliver and Cliff. Great to hear your voices.

Lane: Likewise, Kevin, thank you.

De Cock: Alright, see you all soon I hope. Take care. Bye-bye.

Morgan: Bye.

Q: I only have one really remaining question here and that's in view of some of the discussions and objections to doing the science in the middle of this emergency response, how do you look at in general the actual effect that the science had on the response? How do you evaluate that?

Lane: I think the science that was done had an opportunity to focus particularly some of the US government efforts in the area of what do we do about vaccine, what do we do about treatment, as opposed to there being multiple different things going, at least from a US government perspective. I think we were relatively well focused in those areas. I think one thing it also did, as Kevin mentioned earlier, it brought additional subject matter expertise from the US to in particular Liberia, to a lesser degree Sierra Leone and Guinea. It allowed us to bring NIH-type assets into the field that I think were helpful to some degree particularly in Liberia in helping to provide additional support to some of the public health response.

Morgan: At the end of all this I think the major challenge ahead of us is, how do we reduce the time from once a trial has been conducted and we get information to getting a

product that can be used in an outbreak? Clearly this outbreak was unusual in its size and the length and so on, but it does at least open, in my mind, this question that if we can improve our science investigations during outbreaks, we then need to also have a nimble regulatory process so that if we do find a product is successful, then we can get that into the field. And I think it's a challenge especially because the pace at which new products can be developed is increasing. The technology is allowing us to develop laboratory tests, vaccines, therapeutics at a speed that wasn't possible before, but the speed of getting those products actually out and into the field is pretty much the same as it was. So I think we need to think that through a bit more.

Q: Okay, I think that's a great way to conclude. Thank you so much, Cliff, for joining us. I don't know if you had any final reflections or memories on your time especially with Oliver, Frank or Kevin that stand out to you.

Lane: No. All I would say is that we could not have done what we did without Kevin, Frank and Oliver in that order in terms of temporally but in terms of content. Every single one of them was just an exceptional partner and we are so grateful that we were able to work with them.

Q: Oliver, anything to add?

Morgan: Only to echo how gratifying the partnership was. We're going to find ourselves working together in the future, don't you think, Cliff?

Lane: Yes, I do, and I would just add one additional positive note on to this. We just received word I guess a week or two ago that we had put in a recommendation that the team involved in this be considered for the [HHS Secretary's Award for Distinguished Service], and that award is being given to this group that worked on these studies, clinical research in West Africa. So, again, some recognition by the department of the importance of the work.

Q: Okay, thank you so much. This has been hugely educational and I'm really happy to have it in our records here at CDC Museum. I will send transcripts to all the participants and you can all comment before everything gets archived. Thank you, again, to all our participants. Cliff and Oliver, you are the remaining ones, so thank you.

Lane: Great, thanks.

Oliver. Thanks Cliff. Take care.

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