Ebola Vaccine and Pregnancy

[Announcer] This program is presented by the Centers for Disease Control and Prevention.

[Sarah Gregory] Hi, I'm Sarah Gregory, and today I'm talking with Jennifer Legardy-Williams, a health scientist at CDC. We'll be discussing the effect on pregnancy outcomes for women receiving an Ebola vaccine in Sierra Leone.

Welcome, Jennifer!

[Jennifer Legardy-Williams] Hi, Sarah. Thank you for having me.

[Sarah Gregory] Okay, start off with reminding us of the Ebola situation during the 2014 through 2016.

[Jennifer Legardy-Williams] Oh, so the West African Ebola outbreak was unprecedented in magnitude and complexity. It first was reported in Guinea in March 2014, and eventually spread to the bordering countries of Liberia and Sierra Leone. One alarming aspect was cases were starting to surface in Conakry, the capital city of Guinea, and this was the first time a transmission had been reported in a major city. Other transmissions were in small, rural, remote communities and, with this transmission being in an urban setting, it had far-reaching effects on their travel and trade and was jeopardizing an entire region of Africa to the point that it could spread rapidly along with a large…largely affecting populations. People were literally dying in the streets. Families and communities were shattered due to this deadly virus. Daily routines were altered because curfews were imposed, such routines as banks closing, schools were closed at months at end, and people lost their jobs. As a result of high death tolls, WHO declared a Public Health Emergency of International Concern, which basically says that we need to have an international response to this outbreak. At the end the end of this outbreak, there were approximately 29,000 cases, 11 deaths that were reported in all three of these communities.

[Sarah Gregory] How many deaths?

[Jennifer Legardy-Williams] There were 11,000 deaths.

[Sarah Gregory] 11,000…okay.

[Jennifer Legardy-Williams] 11 deaths…11,000 deaths reported in all three of these countries.

[Sarah Gregory] Explain to us what a vaccine trial is like in a crisis situation. Usually vaccines take years to be approved.

[Jennifer Legardy-Williams] Yes, that's true. Conducting a vaccine trial during an international epidemic is like building a plane while flying through a storm. It's less than ideal. Clinical trials are usually conducted in well-established research centers where the staff are well-versed in operations and regulations as it relates to conducting investigational new drug trials. However, STRIVE…we did not have that opportunity.

[Sarah Gregory] What's STRIVE?

[Jennifer Legardy-Williams] STRIVE is the Sierra Leone Trial to Introduce a Vaccine against Ebola. That was the trial that was conducted in Sierra Leone. And Sierra Leone, at the time, it…their infrastructure was not in place. Technology was less than ideal. Their medical system was severely compromised because of the outbreak. And so, as STRIVE was being built, we had to partner with different contract research organizations, other U.S. federal agencies, as well as

the CDC Foundation to establish the research centers and data management centers, as well as establish cold-chain facilities throughout various districts in Sierra Leone. And, we were also able to hire and train over 350 staff in the country, which from that we…we find that to be a success that we were able to build a trial so quickly with…

[Sarah Gregory] Over what time frame?

[Jennifer Legardy-Williams] It was a matter of…probably about four months, we were given.

[Sarah Gregory] That's remarkable!

[Jennifer Legardy-Williams] Yes. And so, we feel very proud of that, that we were able to build and implement infrastructure that, if a storm ever happens again—which we don't want that—Sierra Leone is ready and equipped to conduct a trial like STRIVE.

[Sarah Gregory] So all that quickly built infrastructure remains?

[Jennifer Legardy-Williams] Yes, yes.

[Sarah Gregory] How did this Ebola trial come about?

[Jennifer Legardy-Williams] So, in September 2014, WHO convened a meeting of partners which included representatives from all the three highly affected countries, research organizations, public health authorities, and other partners…one a potential Ebola therapies and vaccines. And from that meeting, one recommendation was they wanted to accelerate the development of vaccine and safe use as rapidly as possible in Ebola-affected countries. And so, with that, CDC staff traveled to Sierra Leone in October 2014 to meet with people within the Ministry of Health and Sanitation in Sierra Leone, the College of Medicine and Health and Allied Sciences, as well as the University of Sierra Leone, to see if we could implement a trial during an Ebola outbreak in an effective, efficient way, without disturbing the public health response. And from there, STRIVE was born.

[Sarah Gregory] I see. And did you go?

[Jennifer Legardy-Williams] So, no, I did not…go initially. But in June 2015, I did go in to see how the trial was running, to make sure that the study operations were flowing properly, given that we were starting fresh with this research center.

[Sarah Gregory] I just find it amazing. What kind of vaccine was produced, and what kind of strategy was implemented? And also, where was it done during the initial outbreak?

[Jennifer Legardy-Williams] The vaccine used in this trial is a vector vaccine, which uses a genetically modified version of a vesicular stomatitis virus by inserting a gene of the Ebola virus. This causes the immune system to respond as if the VSV surface is Ebola. But people cannot get Ebola from this vaccine. And so, some of the strategies that were used were…there were three trials conducted in…one in each of the highly affected countries Sierra Leone, Liberia, and Guinea. Two were phase II-III trials, and one was a phase III trial. And so, from that…those data that were collected in those trials, it allowed FDA as well as the EMA to review and approve this vaccine for licensure, as well as WHO, for prequalifications.

[Sarah Gregory] Okay, so you mentioned phases of vaccine trials. Can you explain to us what those are, please?

[Jennifer Legardy-Williams] Sure. Actually, within…with any product with any investigational product there are four phases of clinical trials. One being what is considered phase I, where researchers are looking at the investigational product within healthy individuals. There are about 20–80 healthy individuals that are enrolled in the trial. And they're really looking to see how the product interacts with the human body from the type of way the product is absorbed, metabolized, or excreted from the body, and then also side effects.

[Sarah Gregory] So you're talking about injections like you would get?

[Jennifer Legardy-Williams] So, this…this is for any product. So, if you're talking about a vaccine, yes, if it's an injectable vaccine that they are looking to see how the product actually is interacting with the body in terms of absorption, like I said, excreting it, metabolizing it, but also the side effects associated with the product in terms of the various dosage that may be administered to an individual. And those trials usually take a couple months to conduct.

And then, if the product seems to be…not toxic, then it may move on to a phase II trial, which the…now, a researcher is looking to see how safe the product is within individuals who may have the disease. And they usually enroll about several hundred individuals, and those studies take about several months to two years to conduct.

And then, after that, is the phase III trials, where there are about 300 to about 3,000 individuals with the condition or the disease that may be enrolled in a trial. And they are looking for the effectiveness of this product, and also whether there are any adverse reactions that may occur as it relates to this product being used. And those trials usually take about one to four years. And then, once FDA assesses the profile, the collective profile, of this product and they decide to approve the product, there is a…a trial called a phase IV trial, which is basically post-surveillance marketing trials in which they continue to monitor the safety and effectiveness of the product, after it's been marketed.

[Sarah Gregory] And how long does that phase last?

[Jennifer Legardy-Williams] It depends on the product.

[Sarah Gregory] Who volunteers for these? Especially early ones…

[Jennifer Legardy-Williams] Students…anyone that has an interest in being involved in a clinical trial can volunteer, if they meet the exclusion/inclusion criteria.

[Sarah Gregory] How many doses were administered? And, obviously, was it successful?

[Jennifer Legardy-Williams] Yes. This was definitely a successful trial. We enrolled 865 participants and administered 8,000 doses. One goal of STRIVE was to potentially provide protection to people in the most highly affected areas of Sierra Leone. And from this trial, we were able to provide the largest amount of safe…safety data of the West African trials. It really helped for FDA and EMA to be able to assess the safety of this vaccine when they were reviewing it for licensure.

[Sarah Gregory] Okay, so it was a success. Was it then later expanded to use the vaccine other places?

[Jennifer Legardy-Williams] There were no cases of Ebola within STRIVE participants, because the epidemic came under control during our trial. This was great news, but it did mean that we weren't able to measure efficacy. However, in the Guinea trial, they were able to demonstrate

that the vaccine, which we call rVSV-ZEBOV, was highly effective in protecting against Ebola. And so, based on those findings, they were able to use this vaccine in later cases in outbreaks under expanded access and compassionate use protocols.

[Sarah Gregory] Is it still being used?

[Jennifer Legardy-Williams] Yes. It's currently being used in the Democratic Republic of the Congo's outbreak.

[Sarah Gregory] Can this vaccine be given after someone has been exposed? Or does it have to be before a person is exposed?

[Jennifer Legardy-Williams] Now, like other vaccines, this vaccine is administered prior to exposure.

[Sarah Gregory] Because I think rabies, right? If you think you're exposed to rabies, you can get the vaccine.

[Jennifer Legardy-Williams] That is true, but…

[Sarah Gregory] Not this one?

[Jennifer Legardy-Williams] Not this one.

[Sarah Gregory] Oh, too bad. Okay, so why don't you give us some details of this study now.

[Jennifer Legardy-Williams] So, what I'll do is I'll explain the overall trial and then describe the pregnancy aspect, so that you can better understand all the intricacies of the study.

[Sarah Gregory] Okay.

[Jennifer Legardy-Williams] So, STRIVE was a phase II-III, unblinded, which means that you know whether you're receiving the vaccine or not. It was no placebo, meaning there is not a fake vaccine given or something that was substituted, and it was randomized. So that meaned that people that were enrolled either received the vaccine immediately or within seven days of enrollment, which we call the “immediate group,” or they could be randomized to receive the vaccine 18 to 24 days after enrollment and they were called “deferred vaccination group.” We enrolled healthcare workers and Ebola frontline workers because they were at the highest risk of exposure at that time, and all participants who were enrolled were followed monthly for suspected Ebola, adverse events, and pregnancy outcomes. And the overall safety profile for STRIVE was like other trials using rVSV-ZEBOV. There was no vaccine-related serious adverse advents, which includes deaths, for the trial.

In terms of the pregnancy aspect, at screening, we screened women who were between the age of 18 and 49 years of age. We asked them whether they were pregnant at the time of screening, and then we administered a urine pregnancy test. So, for women who were vaccinated, they were counseled to avoid becoming pregnant within 60 days of vaccination. Within the trial, we did not provide contraception for these women, but contraception was available through family planning clinics and services. If a woman who was…their estimated date of conception was within 60 days of enrollment or vaccination, they were followed monthly by study nurses until their pregnancy outcome was documented.

For our pregnancy outcome, we split the groups into two groups. One was considered high viremia risk, which is if their EDC, the estimated date of conception, was prior to vaccination or

0–14 days after vaccination. And then the second group was low viremia risk, and that was if their EDC was 15 days plus after vaccination. And we did this because studies have shown that in healthy adults, viremia or PCR positivity peaks 1–3 days after vaccination and resolves 17–14 days after vaccination. And so, for our analyses, we only compared the immediate vaccination women with unvaccinated women. And we primarily did this because there are multiple time factors that can influence what our results were going to be, and those time factors, which we call "confounding factors," were the attitudes to pregnancy during the outbreak compared to after the outbreak; whether there was access to healthcare during, compared to after the outbreak—because, keep in mind the infrastructure the medical infrastructure was pretty compromised at the time, so we wanted to account for that. And then, also, there are some infections that have strong seasonal patterns, like malaria, that we wanted to take into account in our analyses. And for the viremia risk analyses, we looked at the immediate group of women and then we looked at the deferred vaccination group, and we did a separate analysis to look…to control for the confounding that I spoke about earlier, as well as we combined them because we had a low sample size.

[Sarah Gregory] You mentioned viremia. Tell us what that is.

[Jennifer Legardy-Williams] So, viremia is when the virus is found in the blood and, as previously mentioned, studies have shown the presence of virus from the vaccine peaking at 1–3 days or resolving 7–14 days. So, when we're talking about the virus, it's really the vaccine virus. It's not the Ebola virus that we're seeing in the blood. It's related to the vaccine.

[Sarah Gregory] Okay. So, the women with viremia are the women that have been vaccinated, and how it affects their pregnancy.

[Jennifer Legardy-Williams] Correct.

[Sarah Gregory] Pregnant women were supposed to be excluded from the trials, why was this?

[Jennifer Legardy-Williams] Because there was little known about the safety of this investigational vaccine. And there had been a safety hold placed on one of the phase I trials because of reports of arthritis in joints distant from the injection site. So, there was a real concern that the placenta or fetus could be impacted. So women were…who were pregnant or breastfeeding were excluded from the trial.

[Sarah Gregory] Okay. And…and why did you want to do this study?

[Jennifer Legardy-Williams] Pregnant women with EVD infection have not fared well, with high rates of maternal infant deaths being reported. And given that we had a small group of women who were pregnant or became pregnant during the trial, we had a rare opportunity to assess the safety of this vaccine related to pregnancy outcomes and potentially provide valuable information.

[Sarah Gregory] So, what went wrong? Why were pregnant women being vaccinated?

[Jennifer Legardy-Williams] We administered urine pregnancy tests prior, as I previously discussed, during the screening phase. But there was a small segment of women who were early in their pregnancy, and so the urine pregnancy test was not able to detect that pregnancy. And then there were some that we believe were administered a pregnancy test and it was not done correctly.

[Sarah Gregory] What were the results? How did these vaccinated women fare?

[Jennifer Legardy-Williams] We enrolled about 3,100 women of childbearing age. Of those, 84 women were pregnant with an estimated date of conception within 60 days of enrollment or vaccination. And, we had 51 live births, 30 pregnancy loss, and there were 3 women we don't know their…the outcome of their pregnancy. Of those 51 live births, we were able to examine 44 infants for congenital anomalies and we did not detect any. Remember I explained earlier our comparison of the immediate and unvaccinated group, and what we saw was 45 women in the immediate unvaccinated group experienced a pregnancy loss compared to 33 in the unvaccinated group. However, this difference was not statistically significant, given that the study was unblinded, and one thing to note: In Sierra Leone, induced abortions are illegal, so women could have been pregnant and had an induced abortion and didn't report it to us, or they could have reported it as a spontaneous abortion. And so, although the rates of pregnancy loss was high in the vaccinated group, it's not clear if this was a real difference or not.

For the viremia, we saw pregnancy loss about 35 percent compared to 40 percent with high viremia versus low viremia, respectively. And then, for the women you were asking about, the ones that were pregnant prior to vaccination, there were nine women compared to eight women who became pregnant 0–14 days after vaccination. There was no difference in live births or pregnancy loss amongst the two groups.

[Sarah Gregory] There were 7 adverse maternal events, were these caused by the vaccine?

[Jennifer Legardy-Williams] No. So, five of the serious adverse events were hospitalizations related to pregnancy complications. One was due to enteritis, and one was malaria. And so, we had all of our SAEs evaluated by experts, and none of them were determined to be associated with the vaccine.

[Sarah Gregory] Why is this information in this study important to the Ebola situation and public health in general?

[Jennifer Legardy-Williams] Given the current outbreak in the Democratic Republic of the Congo, which rVSV-ZEBOV is playing an integral role in the response, it underscores the urgent need to understand the safety of the vaccine in pregnancy due to the high risk associated with maternal and fetal deaths in Ebola infections. Our results, although they were not conclusive, provide valuable information to allow national regulatory authorities and ethics committees as well as WHO to make decisions about offering this vaccine to pregnant women during an outbreak response.

[Sarah Gregory] Is there anything else relating to this study you'd like to tell us about now?

[Jennifer Legardy-Williams] I think one thing to keep in mind about our study, it was a small sample size, which highlights the need for additional comprehensive and accurate pregnancy outcome information. And we would be able to get this through other clinical trials or observational strategies, like pregnancy registries, or even during collection of data through outbreak responses like in the DRC.

[Sarah Gregory] What's your job at CDC? You're a health scientist. What is that and does it relate generally to vaccines? And also, what do you enjoy most about it?

[Jennifer Legardy-Williams] As a health scientist, my primary job at CDC is as a human subjects advisor for the National Center for Immunization and Respiratory Diseases. I still play a role in STRIVE, as the implementation lead, but as a human subjects advisor, I evaluate research and nonresearch activities for scientific integrity, soundness, ethics, and regulatory compliance. And

I think the most exciting part of my job is making sure that we, as scientists, are maintaining the public's trust when we're conducting research and nonresearch activities, that eventually we're going to generate data and information that impacts their lives.

[Sarah Gregory] Well, thank you so much for taking the time to talk with me today, Jennifer.

[Jennifer Legardy-Williams] Thank you for having me, Sarah! I enjoyed talking to you as well.

[Sarah Gregory] And thanks out there for joining me. You can read the March 2020 article, Pregnancy Outcomes among Women Vaccinated with rVSV-ZEBOV-GP Ebola Vaccine during the Sierra Leone Trial to Introduce a Vaccine against Ebola, online at cdc.gov/eid.

I'm Sarah Gregory for *Emerging Infectious Diseases.*

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