On-screen: Trials and Tribulations: The Journey to a Maternal Group B Streptococcus Vaccine Rebecca Kahn, PhD, MS EIS 2022. April 23, 2024 Sarah Luna Memorial Ted-Style Talk Session 2024 Epidemic Intelligence Service Conference. CDC logo on bottom right

(Applause)

REBECCA KAHN: In May 2023, I got a call that changed everything. Now, you might be thinking this call was about an emerging outbreak or a natural disaster, the traditional emergencies that EIS officers deal with, but not this time. This urgent call was about statistics. It was about the urgent need for a new statistical method that would be make or break for a maternal group B strep vaccine. Now, my team had been working on such a method for some time and I had what I thought was a leisurely EIS project to run some simulations to help test out this method. I had experience running simulations as part of my PhD, so I felt ready, but little did I know that this leisurely EIS project would turn into the full court press that then ensued.

If we didn't succeed in applying our method to a real world data set by September, just four months later, the vaccine trials would not happen and there would be no vaccine. Group B strep is a bacteria that increases risk of maternal death and causes over 300,000 infants worldwide to suffer from sepsis and meningitis annually. It also causes an estimated 57,000 stillbirths and 90,000 infant deaths annually. 90,000 infant deaths, that's the equivalent of an entire University of Georgia football stadium full of babies dying every single year.

When I started EIS, I barely knew anything about GBS. By September 2023, GBS consumed an alarming proportion of my thoughts. In my work life, we were working frantically towards our deadline and preparing to present our methods and results to the FDA so that the vaccine trials would move forward. In my personal life, I was waiting for the results of my own GBS test. I was eight months pregnant and if my tests were positive, as it is for about 1/3 of pregnant people in the US, I would have to make sure I got to the hospital early enough for my delivery to

receive antibiotics to prevent the GBS from harming my baby. And these antibiotics would only protect him against disease in his first week of life, he would still be at risk for disease later on in his infancy.

Now, this was just one more thing to worry about on top of all the worries that come with pregnancy. And I just kept thinking how nice it would be if there were a vaccine I could have gotten to protect us both. During EIS, I've joined a team of people who have been working for decades towards a maternal GBS vaccine. Despite development of promising candidates, these vaccines have failed to progress to phase three evaluation trials for a number of reasons. For example, there are big concerns about conducting research in pregnant people. In addition, because thankfully GBS disease is rare, traditional vaccine trials would require too large of a sample size to be feasible and the trials would be prohibitively expensive.

So in 2018, regulators indicated they'd be willing to license the vaccine based on a different type of

trial. Instead of measuring if the vaccine prevented disease itself, the trial can measure if the vaccine helped people create enough antibodies to protect them against disease. So the big question then became, how much antibody is enough antibody to protect against disease?

Now, normally this is where I would discuss the established methods for answering that question, but none yet existed for exactly what we needed to do. My team had been working on a method, but it had never before been applied to a real data set. So back to that May 2023 call. Several vaccine candidates were near ready to interface three evaluation trials and industry sponsors were under time pressure to launch the trials or quit, but there was still no answer to that key question or establish methods for how to answer it. The opportunity to get to a trial depended on our team finalizing our method and applying it to a real data set.

So I want you to just imagine for a minute what this was like for our team. Decades of work leading

towards this vaccine, all dependent on our work and if we didn't succeed, we would miss the window of opportunity for this vaccine. Over the next few months, our team worked to meet regulator's requirements and industry's urgent timeline to ensure that this critical work move forward.

Over the past several years, our team at CDC has been leading a study to try to answer that key question of how much antibody is enough antibody to protect against disease. This case control study conducted in eight U.S. states involved enrolling infants with GBS disease and without GBS disease and comparing their antibody levels. Through this study, we had data on hundreds of infants, so that was the first piece of the puzzle.

The second piece of the puzzle came from our team statistician, Nanjing [phonetic]. Now, if you want to hear the details of the method he developed, come to my talk on Thursday, but I will give a high level overview here. Essentially, because our study wasn't randomized, we couldn't just analyze the antibody

data on its own. We had to think about potential confounders or variables that could distort that relationship between antibody and disease. For example, pre-term infants might have lower antibody levels because they spend less time in utero and they may also be at higher risk of disease regardless of antibody level. So we needed to account for this in our analysis, but methods to do so just didn't exist.

So Nong [phonetic] and our team worked to develop a method, test it out, and apply it to our case control study. And thankfully, because of the careful design of that study, we had detailed demographic and clinical data on all the participants. So, now we had antibody data, covariate data, and a method to analyze them together. We then worked quickly to analyze the data and present the results to the FDA so that the vaccine trials will move forward. At times, it definitely didn't feel achievable and we felt extra pressure because the other studies that FDA expected to rely on just didn't have the sample size they had expected to inform decision making in the way they had hope. It was really up to us.

Back in my personal life, I was also feeling a lot of pressure to get ready for our baby. We were spending weekends assembling furniture and trying to get everything prepared. I hoped he wouldn't come early so that we would have time to get everything done and also, because our meeting with the FDA was scheduled for September 27th, just three days before my due date of September 30th.

Thankfully, our team was able to meet our deadline and we presented the results to the FDA. And because of the critical implications of our findings, the World Health Organization organized another meeting for us to share our findings with additional regulators. And now they're awaiting the results of our final analysis that will have a larger sample size and allow for final decision making.

Thanks to our work, there is now a clear path for the vaccines to go to trial and the companies didn't quit. If they are successful, there will be major public health implications and lives will be saved.

Methods for analyzing real world data like ours, [audio breaks up briefly] increasingly important as -- - when randomized controlled trials aren't feasible. And sharing these methods are developed in advance is critical for public health preparedness.

So now, back to my personal life. Thankfully, my GBS test was negative and my son Ari was born healthy. And he was a few days late, so I was able to lead the presentation to the FDA. Sometimes public health isn't glamorous at all. A lot of times it involves us sitting at our desks, struggling through hard methodological problems and statistical questions. But I hope you can see that statistical methods can be just as exciting and impactful as things like outbreak investigations, because behind these statistics are real babies, real parents, real lives. Thank you.

(Applause)

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