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HIV and Zika in Pregnancy: Past and Present Challenges

Carmen Zorrilla, MD

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HIV and Zika in Pregnancy: Past and Present Challenges

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- [Jim] Welcome to Physicians' Research Network. I'm Jim Braun, the Course Director of the monthly meetings of PRN in New York City. Since our beginning in 1990, PRN has been committed to enhancing the skills of our members in the diagnosis, management and prevention of HIV disease as well as its co-infections and complications. We hope this recording of Carmen Zorrilla's presentation HIV and Zika in Pregnancy: Past and Present Challenges will be helpful to you in your daily practice and invite you to join us in New York City for our live meetings in the future. PRN is a not for profit organization dedicated to peer support and education for physicians, nurse practitioners and physician assistants. And membership is open to all interested clinicians nationwide at our website prn.org. And now, allow me to introduce Carmen Zorrilla Professor of Obstetrics and Gynecology and Principal Investigator at the Maternal-Infant Studies Center at the University of Puerto Rico School of Medicine in San Juan.

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-[Carmen] Thank you for inviting me and good evening. I'm gonna talk a little bit about my experience so far with the Zika epidemic. And as an AIDS doctor who started working with pregnant women living with HIV. It's like I'm going back in time and I'm telling pregnant women, you have a virus. I don't know what this virus might cause. I don't know what this will do to your fetus. There's no treatments, there's not vaccines so we'll have to see what happens. It's like repeating 30 years from time ago. But I do believe that we have something different, which is we have experience.

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We know how we did, how we work against the HIV epidemic and we had major successes, so we should be able to use the same or similar strategies to deal with Zika. Because in my opinion, it is a very serious threat to the next generation of infants.

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That's the curve of prenatal transmission in the U.S. And I know most of you are not obstetricians nor pediatricians, but anyway.

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This is the curve from Puerto Rico and my clinic. The last baby that was positive is a teenager already, was born 13 years ago. And I see about 50 pregnant women living with HIV every year so that's our success story.

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This is sort of controversial. Last July, Show declared that Cuba was the first country to eliminate mother to infant transmission based on prevalence and service of two years. And, let me just refer to this graph. So we're in the process of actually demonstrating and we have policies information that it might not be true that Cuba was the first country to eliminate. But anyway, we celebrate successes of this anywhere

in the world. As I started, I started telling you that I feel there's a parallel between the Zika epidemic and the HIV epidemic. And we do have some successes that we leave with HIV and now we have some challenges that we're confronting with Zika.

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First of all, both of them were new and unknown viral diseases. And they affect fetuses in different ways. Initially, when we started working with HIV there was a report of an embryopathy which is some specific abnormalities on the fetus like fetal alcohol syndrome. That was reported in the early days it was later not confirmed but Zika does produce a if you want to call it, an embryopathy. It's sexually transmitted as well. It's seen as, or perceived as affecting tourism. There are mixed messages in the public response. Some people say this is an invention of somebody to get money, or to gather funds. Some people say they have not seen any person with this illness and so this is something that's not true. Or it happens in other countries, not in our country. I have, I'm leaving their patients have being stigmatized as much as when they had the people with HIV, same as fear, social isolation. I've had pregnant women who've been abandoned by their partners when they have been diagnosed with Zika, right now. We, as I mentioned there's not treatment or vaccines. Prevention is the only means of control. We know what prevention. It's very difficult, especially when we talk about condom use. For heterosexual couples, it's very difficult to actually convince and implement and have people universally adopt that. So, and I think that prevention strategies that need individual behavior changes are the most difficult strategies. And we need systemic strategies that might not need and this is how we had success in HIV with biomedical strategies.

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So, we already have a roadmap and we think we need to be open and honest with out communication. we need to consider all options for vector control and to implement and control the epidemic. We need to have a comprehensive plan and throughout the implementation of the plan we need to reevaluate that response and the strategies. We need to involve communities, involve activists and we also need a fast track pathway for approval of drugs and strategies much like we had when we had the HIV epidemic. So these are all strategies that we already have some experience with them. And I believe right now, for Zika we are not seeing multi-sectorial working groups in some jurisdictions. We are not seeing the use of all the strategies that we could use, and I will mention some. So what's, why am I here? Because in Puerto Rico, we are living in we are in the middle of a Zika epidemic that the first case was diagnosed or reported December 30th, 2015.

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Based on the Chikungunya epidemic that happened three years ago, they have estimated that 25% of the population will get Zika. And that's about 700,000 people with Zika. And if we consider 25% of the 14, 34,000 pregnancy or birth that happened couple of years ago. That means almost 9,000, 8,600 pregnant women might have Zika infection this year. Another issue with Zika infection is that 80% of people who have Zika do not have symptoms. The rash, the all the symptoms only happen in 20% of people. So you can have, I could have Zika. Anybody could have Zika if it's exposed. If he or she is exposed, and might not have any symptoms and transmit it, much like HIV. The estimate of

microcephaly initially was calculated in 1% based on what happened in the Micronesia epidemic. Or sorry, in the French Polynesia. But then with the present epidemic in Brazil it was calculated between 1 and 13%. The risk of microcephaly, if the infection occurs in the first trimester. First trimester is before the first 14 weeks of gestation.

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This is a busy slide, but this is just a recent publication on how they estimated the number of women that could be infected with Zika in Puerto Rico, based on the fertility rates of the population, and the Chikungunya percentage of people that had symptomatic disease. And the baseline prevalence of microcephaly.

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So it's more sophisticated, but it's about the same as if I can tell you that 25% of people can get it. So 180 cases of microcephaly related to Zika infection could be estimated to happen or be reported in Puerto Rico or seen.

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Those are the countries that right now have evidence of Zika virus transmission and infection. Remember that there's global warming and so this tropical diseases, these tropical areas are expanding, so we're now going to be seeing more tropical diseases because of the global warming. And this is one message that when people think they are targeted, oh well it's just Brazil or it's just Columbia, you can say it's in many countries as well.

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So, back to the numbers game. There's a recent publication estimating worldwide billions of people, billions of people. I think it's 10 billion people that could be infected with Zika in the world. The Puerto Rico Health Department reports the Zika cases every Friday. And every Friday, I add one bar to this graph.

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This is the graph of pregnant women in Puerto Rico with Zika confirmed by laboratory. And the policy and the recommendation for Zika testing in pregnancy are based on CDC recommendations. Are in endemic areas such as Puerto Rico now. To test in the first and second trimester of pregnancy whether the woman has symptoms or not. And these recommendations from the CDC respond to the justification of if if you diagnose in the first and second trimester you might have options for pregnancy continuation or interruption. But as you might see from my presentation here. One of my recommendations will be that we need to expand the testing to the third trimester, and maybe to delivery. Because now the testing is not for making decisions regarding pregnancy, but the testing is to identify potentially affected fetuses. And to identify exposed infants and to follow them. If we don't test, we don't know they have it. So it's not going down, this curve. this is why I'm saying that we should reevaluate our strategies, because we've been like nine months on this epidemic and this is what we're seeing.

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Every Friday, they have this map and the darker the color, the more cases and these are the 79 municipalities in Puerto Rico. In terms of, every town probably has Zika. So as of last Friday, there were 17,871 confirmed Zika cases by laboratory. And of those, there were 15,000 pregnant women. And of the pregnant women, one third of them, about 535 had not had symptoms. So that means they were tested because they were pregnant. And we identified them because we're testing. So this is something good. We're testing, we're identifying one third of pregnant women with Zika have no symptoms. There was a microcephaly case. And there have been two deaths already. And 45 cases of Guillain-Barre.

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So in terms of our response to the epidemic we establish being located in a high-risk area with a tertiary care hospital. We established a multi-disciplinary clinic for pregnant women with Zika infection. Very much like what we do for HIV. We have to have resources and combine resources and strategies, so whatever I was doing for HIV that was exactly what I started to do with pregnant women with Zika. And the other thing that I did, which is different is that I approach the program of clinical psychology because I believe that being pregnant in the middle of a Zika epidemic is just too much stress. And so, just to deal with the stress and stress id directly related to pre-term birth and low birth weight. And I eliminated some of the slides that I had here on pre-term births seen in New York City after 9/11. Immediately after that year, there was an increase in pre-term births and low birth weights not just in the city, but in the State. And it was just related to the stress that we all lived with the Twin Tower events. So we started that, we approached this program of clinical psychology. And now we have doctors, students of clinical psychology in the clinic, with the obstetricians with the residents, with the women as well. And the next thing we did is that we pursued to participate in research because we need to understand what happens with this infection. So this is the ZIPS, Zika in Infants and Pregnancy Study.

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It's sponsored by NIH and Oswaldo Cruz Foundation in Brazil. It will recruit 10,000 pregnant women in the first trimester in two years, in Columbia, Costa Rica Brazil, Puerto Rico and Nicaragua. So far, five countries who have Zika epidemics will recruit women in their first trimester. We will start testing these women. We will do IGM testing every month. And we will collect samples of urine every two weeks so that in case that we have a positive IGM test on a blood sample, we can go back. Two weeks back to the urine sample and we can actually say when this woman got infected during that pregnancy. And then we will follow the pregnancy and identify if there's adverse events related to the timing of the infection. Whether there were symptoms or not. Perhaps this is a good time to say that there is no IGG test. This is one problem so that we can not identify who is immune to Zika long term. IGM will be present for three months. PCR might tell you that you had an infection now about 10 days, and if you do PCR in urine you can actually go to a wider range of two weeks. So you can either identify recent infection or active infection with PCR in urine or blood. Or you can identify relatively recent exposure to infection with IGM, that would be three months. But beyond that, we do not have any tests that can tell me. For example, I have a, I'm right now following a pregnant woman who had Zika infection had a spontaneous abortion, it's one of your cases. And she came and asked me. She had Zika on that event in May, last May. And what do we do with her? What does it mean to have a positive test now? What does itmean

to have a negative test now? So we believe that person who has been exposed and infected with two Zika. They develop immunity and they, it will not repeat. The problem is that you cannot know who has immunity because we do not have the IGG. So if you can identify by acute infection PCR or IGM, you can know that in the future this person might not repeat the infection. As with Dengue that we have four serotypes. Zika is just one virus so this is why we believe there's immunity.

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So the ZIPS study, as I mentioned we're going to compare the incidence of adverse events, fetal outcomes. We're gonna compare the incidence of fetal malformations among the women, with and without Zika. And with Zika with symptoms and Zika without symptoms.

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The most benefit for these women, at least in our study is that they will be regularly tested for Zika since it is symptomatic, we will be able under one study a natural history study to identify exactly who gets infected and when.

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So general inclusion criteria, older than 15, consent and confirmation by ultrasound and dates that she has the pregnancy less than 14 weeks. Let's move on. So what do we know about Zika and pregnancy? Everybody thinks about the microcephaly which is the extreme. By the way, the definition of microcephaly is fetal circumference that's in the third percentile of the size. That third percentile, that's really extreme. But what if it's in the fifth percentile, is it normal? Not necessarily, right. So we're defining something by an extreme and this is how we got to get to the Zika because microcephaly is very rare and Zika was very rare and there we had these two events and this is how the association was made.

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But late onset post-natal microcephaly has been reported already. There were babies that were born with normal-size heads whose mothers were infected in the last trimester and by six months, the rest of the body grew and the head didn't, and so that proportionally now they have microcephaly that was developed or evidenced post-natally at six months of age.

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There's a study from, an early study from 88 women who came with symptoms in Brazil. And they were tested, 82% had Zika and of those, one third of the ones who had ultrasounds had abnormalities. And the most worrisome thing for me is that two mothers presented with intrauterine fetal deaths. One fetus at 36 weeks, that's about 8 months pregnancy and another one at 38 weeks, that's about, that's term. So two fetuses died in utero. We do not know if it was related to the Zika but out of 88 pregnancies, we have two fetal deaths in the third trimester, that's very rare. So this is my message when I talk to women. It's not just protecting yourself during the first trimester it's that you have to protect yourself throughout the pregnancy. This can have different impacts.

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So we talked about the microcephaly we talked about the still birth. There's ocular abnormalities and other abnormalities. I want to show you what do we do if we identify we have to follow with Level Two ultrasounds every three to four weeks.

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Level Two ultrasounds are targeted to organs. We will measure the brain, the heart, the kidneys it will go every organ. So that's a Level Two ultrasound. This is data presented by a colleague of mine. Doctor Alberto DelaVega in a recent meeting and so

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he did an analysis of about 200 pregnant women that he did Level Two ultrasounds. And that they had Zika and they knew exactly when they had the symptoms. And he also compared this information and the fetal circumferences and the sizes of the fetus to the normal fetuses in the unit which is about a thousand infant or fetuses.

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He found intracranial calcifications ventriculomegaly, growth above the median. On some, head below two standard deviations of the mean. Head below three standard deviations that's the definition of microcephaly, none. Abnormalities in several artery flow IUGRs. Abnormal placental calcifications. You have Oligohydramnnios and intrauterine fetal deaths, two. So there's different things, a lot of things that we identified abnormal among those 128 patients. So he did this head circumferences on all the fetuses at the University hospital. And he compared this curve with a normal curve for the U.S.

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So you see the lines overlap. So our infants, our fetuses have the same size of head circumference as the fetuses in the U.S. So we can say that the growth curves are okay. We can use the published growth curves.

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And these are head circumference size of 27 fetuses who had an infection in the first trimester. If you see, most of these fetuses head size are within normal but all of them are below that line. None of them are above as per this line, the normal line you see dots above and below. This one you see. And this is a visual. My presentation here is visual. Just look at the dots below that line. Same thing for fetuses infected in the second trimester.

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There was a little bit more distribution, wider distribution but most of them also fell below the line but still within normal. Understand they are still between the normal deviation. And fetuses who contracted it in the third trimester.

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So when he compared head circumferences of infants who had Zika in the first trimester with the other infants you see that again most of them are below the normal curve.

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There's this, a little bit better distribution if the infection was from 18 to 14 weeks. A little bit better distribution if the infection was after 8 weeks. So it seems that we're looking at impact on head size according to gestational age where the infection happens, but still we're seeing normal, within normal. We cannot say there is microcephaly here.

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So what happens when we compare the abdominal circumferences of the fetuses with Zika infection, compared to the normal other fetuses. You don't see these differences. You see the dots above and below. There's no impact on the abdominal circumference. And believe me, it's not here but there's no impact on the femur length. So it seems that we're having some impact on the head size but not on the rest of the body. Of course, this virus is neurotropic, it's doing something. We don't know what the impact of this in terms of post-natal growth, or the development and all of that. We're seeing subtle changes in head size. We don't know the significance of this in terms of infant outcomes.

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As I mentioned, I approached the School of Psychology because I believe that it's very important to provide support. And just to, I'm gonna mention this is the experience of the pediatricians with Chikungunya so this is not Zika. But these were babies whose mothers had Chikungunya five days before delivery

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or more than five days before delivery. And the ones whose mothers had Chikungunya before delivery five days had chikungunya, had symptoms. But the newborn whose mothers had Chikungunya much earlier had other abnormalities like hydrocephaly and brain infarct. This is what we have seen on the small number of cases of exposed infants that have been born in our hospital.

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We had one patient who's spontaneous pneumothorax. Two patients with Optic disc hypoplasia and retinal bleedings, and one Arachnoid cyst. So even of 14 cases of infants born normal size we're already seeing some abnormalities that are of concern and that I believe that will indicate that we need to evaluate these infants better.

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These are like stress tests, anxiety and depression. We're still not seeing significance in terms of the patients who do not have Zika versus the patients who have Zika. But there are some trends in terms of percentage of high stress among Zika versus none. But the numbers are really small when we did this. There is a modeling of Zika infection

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and the virus infects all the cells of the placenta. So the placenta becomes a culture medium for Zika. So this is why pregnancy is different than the non-pregnant state. In a non-pregnant person, you can say the infection is over in ten days. In a pregnant person, you cannot say that because you can have virus multiplying in that placenta. And of course there's the study on the risk of microcephaly.

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This case was a Zika microcephaly reported microcephaly case here from the New York Tri-State area. I'm showing this because I met this reporter sometime ago and she wrote this story and she went to Brazil and interviewed the women with babies with microcephaly. And she said that the pediatricians were really challenged because the women would come to the clinic. Let's say one week or two weeks later saying

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the head is growing the hair is growing, it's a miracle. And what's happening is that the head is accumulating fluid. So the heads are not growing but they are developing hydrocephalous and so this is really, it might be a challenge to us. Their Zika can live in semen

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for 68 days. And so a man who has had infection can transmit the infection for that long. And so the recommendations are to wear condoms even three months after those 60 something days. So now we're talking about six months of condom use after a Zika infection in men. Transmission through breast milk has not been reported yet.

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But there were four cases of mothers who had Zika infection and this was from the French Polynesian epidemic. These women had Zika the week before or around their delivery. The babies developed Zika in the first week of life. So they, this is how they interpret it that these babies acquired the Zika peri-natally. But these mothers had PCR positive on breast milk. So I'm just waiting, I believe that as in many other viral infections. If the virus lives in other tissues and secretions we might have transmission of Zika by breast milk. The WHO recommendations right now is that breastfeeding is recommended to everybody. And of course, and I'm actually seeing women who are breastfeeding, who are postpartum and have acute illness. And that person has to stop breastfeeding with that fresh milk. They can use their spare breast bank that they have frozen while they recover from the illness. And I have already seen a couple of cases like that. But it's a matter of time. So in terms of transmission there's no transmission reported by breastfeeding but it might happen. So in terms of questions, breastfeeding is not a route of transmission so far. Blood, sex, care-taking and

[audience member] Mosquitoes

--[Carmen] I must, the vector, yeah let's get the vector.

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Another concern is that there’s reports of schizophrenia at age 26 on infants whose mothers had viral

diseases when they were in utero. Pregnancy termination is an issue. It's an option, it's legal in our country.

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There's many studies that have shown that women go through very difficult periods making the decision but once they make the decision, the stress is over.

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Yeah, maybe you can see this. This is a portal of monkey studies where they infected a pregnant monkey with Zika in the first trimester. And they demonstrated that for 79 days they could measure PCR in the pregnant monkey blood. So that's what I was telling you that my hypothesis is that this virus can live in the placenta and can keep multiplying. Can also multiply in fetal brain. So this is why we have long term levels of PCR positivity on this case, the pregnant monkey.

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There's studies on Rhesus monkeys where they infected them with Zika and then they challenged them with a second infection and they were protected. So there is evidence from animal studies that there is immunity. The other evidence is from epidemiological studies that once that epidemic happened in Micronesia. It infected 80% of the people, it was not you didn't see, it was when over there were no additional cases because most people had immunity.

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Strategies for vector control. These are, they are called AGO traps. These are mosquito traps and they have been studied in Puerto Rico. And they have been studied for several reasons. One, to see whether they can capture mosquitoes like to study whether these mosquitoes carry whatever. And another one is whether these traps can reduce the number of mosquitoes in a household so that they can prevent illness. There are two reports. One, that it does reduce the population of mosquitoes. So it actually works trapping mosquitoes. And it also prevented, or reduced the risk of Chikungunya by 50% in households or communities that had three of these traps inside of the house. So my question is again. I started this talk saying that we need to do,

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evaluate our strategies. We need to have a fast track for approval of strategies and I do believe that we need to have a fast track approval for these types of gadgets that can that don't need individual performance or behavior change and can reduce by 50%, the number of infected and ill people in an area. So I think an AGO trap might work better than condoms if people don't wear the condoms.

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These are photos of these traps. They look like paint cans to me. They don't seem so complicated or sophisticated. And they certainly do not affect the environment because they're just trapping mosquitoes and larvae.

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There's another strategy, it's called sterile insect technique. And this is a strategy, where by different

means either irradiation, genetic manipulation or infection with a bacteria called Wolbachia that occurs in 65% of species in the wild. The male mosquitoes become infertile and then you breed these male mosquitoes and then you release them. They mate with females in the wild and they cannot multiply. And in eight weeks, you can actually eliminate the population of whatever insect. This has been studied for other insects not just mosquitoes. For the fruit fly, for other insects in agriculture. So this is a more complicated and costly strategy that again, needs to be studied. I should tell you that when I was a medical student there was this weird professor that you know, he was an entomologist. And we look at him like he always was wearing a wrinkled coat and he looked like very weird and strange. And we as students, we laugh at him. Oh, look at that guy, he publishes in mosquito news. And guess who's reading mosquito news now. In my department, we actually had a faculty meeting and came up with some recommendations.

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And we actually, as I mentioned we want to have a multi-sectorial commission or work group. We want a fast track process for the approval of strategies. We want actually, these traps. There is a pilot study of these traps right now in Puerto Rico. I think we should not do a pilot study. I think we should be implementing the traps or distributing the traps all over.

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The lab reports, the laboratory results are also taking longer than what people want to. So these are things that we want also to impact on the testing. Certainly we want testing to be expanded to the third trimester and delivery if the patient has not been tested. And of course if there's symptoms that's another reason to test.

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And then the AGO traps, and also we also recommended that these other technologies need to be studied. You need to understand that the mosquito that's our enemy here is Aedes and not Anopheles. The Anopheles mosquito carry malaria. Just take this in, just remind of this because when you're answering some questions in the future you might be confused between Aedes and Anopheles. And so, a need to understand that there's no IGG test for Zika as well. And that IGM and PCR are the only ones that we have right now for testing people. And that, if a person develops Zika this person is protected from future Zika infection. So I will end with my favorite quote and that's actually Air Force One.

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In Puerto Rico, I took that photo from the balcony of my apartment so that's why it's there with the landing gear. None of us knows what might happen even the next minute yet we still go forward. Because we trust, because we have Faith. Thank you so much.

[Video End]