When Science Finds a Way

Season 2, Episode 5
Pregnancy and research: inclusion in vaccine trials

Show notes

Episode description:

Over the years, the reluctance to include pregnant women and people in vaccine trials has been increasingly challenged. That's because their inclusion can make vital medications available during pregnancy and provide data that could improve survival rates for both parent and baby. Alisha is joined by Dr Flor M Munoz, a global expert in maternal immunisation to discuss a new vaccine trial, safety considerations and the future.

Mentioned in this episode:

Thalidomide - a compound that was developed in the 1950s originally for use as a sedative or tranquilliser, but was soon used for treating a wide range of other conditions, including colds, flu, nausea and morning sickness in pregnant people.

ALIVE Unit - African Leadership in Vaccinology Expertise (ALIVE) is based out of the Wits Health Consortium at Wits University in Johannesburg, South Africa.

Transcript

(Music starts) 00:00

Flor Muñoz CLIP 00:04 - *"The question that people should be asking is 'Why not include pregnant women?' And it needs to be justified why we are excluding pregnant women from a potentially very beneficial vaccine - or medication for that matter."*

Alisha Wainwright 00:23

Welcome to When Science Finds a Way, a podcast about the science changing the world. I'm Alisha Wainwright. And this is where you'll find stories of hope from people on the front line of our biggest health challenges. And 'hope' is the key word today because we'll be hearing about how we're starting to see a shift in how we run medical research - specifically vaccine trials - to make them more inclusive for pregnant women and people.

You'll have seen the labels - 'If you're pregnant or breastfeeding, consult your doctor before using this product' - well, that's almost always because it simply wouldn't have been tested on them and this applies to many vaccines too. Despite changes to guidelines about how and when to include pregnant women and people in drug trials, it's still very unusual to see this actually being done when developing a vaccine. For example, one study looked at 400 vaccine trials between 2018 and 2023 and found that almost 95% of them explicitly excluded people in pregnancy. This can mean no data, which means no clear recommendation about

its use in pregnancy - a problem we still see with the Oral Cholera and Mpox vaccines. But the tide is slowly turning and today we're going to discuss why and where this is happening with Professor Flor Muñoz.

Flor is a specialist in paediatrics and infectious diseases at Baylor College of Medicine in Texas. She has been working on maternal immunisation and maternal vaccines since the 1990s, as an investigator, on ethics boards and as part of safety monitoring groups - and she has been involved in numerous trials which have involved pregnant women and people.

And just to note, we'll be using the terms pregnant women and pregnant person or people, interchangeably. We know the language around this varies depending on location, but ultimately, we're just trying to be as inclusive as possible in this conversation. Flor, welcome to the podcast.

Flor Muñoz 02:27

Thank you so much, Alisha. It is my pleasure to be here with you today.

(Music ends)

Alisha Wainwright 02:31

Fantastic. So, you specialise in maternal vaccines - so immunisations given during pregnancy - why are these so important?

Flor Muñoz 02:39

You know, it has been really the main area of my career - working on vaccines and disease prevention in pregnancy - because I am a paediatric infectious diseases physician, and a lot of what we see in paediatrics has to do with infections early in life - too early for babies to be protected from their own vaccines or from their own immunity, which needs to adapt and grow as the baby grows. And so we have a period of vulnerability, very early in life, in which babies do depend on the maternal protection and you can achieve that through vaccines.

Alisha Wainwright 03:15

Also - just - the human body is so interesting. Well, the fact that you can inoculate a mother and then she can pass on some of those antibodies to her infant to offer some basic protection - that's kind of their first entry point into the vaccination process - these newborns.

Flor Muñoz 03:33

Actually, I'm glad you said that because, you know, I guess here we are talking about this process, assuming that it's exclusive to vaccines, and it's not.

What we are doing is trying to really replicate a natural selection effect, you know, I would say. Because what happens naturally is that babies are receiving from their mother all of the experience - immunologic experience that this mother has. So a mother who has been vaccinated, a mother who has had a particular infection - say chickenpox as a child - is going to have that antibody in her blood circulating. And you know, the placenta is just an amazing

organ. What it does as it grows through the pregnancy, is that it has an active mechanism - so it's almost as a pump - that is going to grab all that protection that the mother has from her whole history in her life and pass it on to the baby.

Because the babies are going to be born, still with an immune system that needs to adapt to the environment, and babies are very, very susceptible in the first few months of life because they don't have that ability to respond. So the babies who receive that antibody from their mother, that's how their survival really is assured, you know, and this is a very natural process. I call it again, you know, like a selection because you really depend on that for survival.

So, you know, there are things like tetanus, for which we don't get exposed very often, you know, ideally - tetanus is not a disease we can treat - but if we give a vaccine to a mother or in addition to vaccines that they've received during childhood, they can increase or boost that antibody level. And so those babies will be potentially exposed at birth, but they will not get infected and die - it's a deadly disease. Same concept has been applied, you know, for the whooping cough - whooping cough we normally don't start giving vaccine to babies until two months of age, but their highest risk of death is in the first six weeks of life. So, we need to get, again, boost the maternal antibody, so babies are born with that.

Alisha Wainwright 05:41

So why have pregnant women and people historically been excluded from vaccine trials?

Flor Muñoz 05:46

I think that what happened was that the decisions to vaccinate pregnant people were based on the risk of the mother or the risk of the baby from a disease, and the fact that vaccines were available - therefore they could be included - but there was no specific research being done. Part of it has to do with concerns regarding the safety of vaccines.

Alisha Wainwright 06:08

Sure.

Flor Muñoz 06:08

And how many other products could affect the pregnancy or the foetus. One example - in the early 60s, 70s - was the story of the thalidomide.

Alisha Wainwright 06:18

Thalidomide, yeah

Flor Muñoz 06:19

Yes. If you recall that.

Alisha Wainwright 06:22

Can you speak on what happened just for those who may not be familiar with this very tragic, tragic instance that happened with pregnant people?

Flor Muñoz 06:30

Absolutely. So I was, you know, just stating the fact that before thalidomide, pregnant women were not really restricted to take medications or even, you know, at that time, smoke or drink alcohol - it was not something that was known to be a problem necessarily. But thalidomide was actually a medication that was used, by some pregnant women, for trying to counteract the very severe nausea that you can have in early pregnancy.

And what happened is that women who were taking this medicine started to have babies with birth defects - a very severe birth defect that is called phocomelia - whereby the limbs of the baby do not develop. So, babies were being born without arms, without legs - you know, with very severe malformations - that were clearly and directly associated with thalidomide.

So that resulted in a tremendous backlash - a lot of concern regarding anything that a pregnant person would take during pregnancy could affect the baby. And it was…

Alisha Wainwright 07:30

Just out of precaution.

Flor Muñoz 07:31

Exactly. So, very extreme precautions so that you would really not have an opportunity to take medicines, or be participating in any type of research, related to anything that could potentially or could be perceived as affecting the foetus.

Alisha Wainwright 07:47

And how has this narrative changed over the last couple decades?

Flor Muñoz 07:51

Well, you know, so the main shift that has occurred is that as more research has been developed and the advantages of prevention of diseases through vaccination are much clearer, more technology is available to develop vaccines that are safer than the vaccines that we had 50 and 60 years ago, and the fact that there remains significant risk for a pregnant person - and her baby - to develop certain diseases, that having participants in research who are pregnant, has become actually a way to protect them and their babies from these diseases. So, we have shifted from exclusion of pregnant participants in research to actually including them, so that they could not be left out or left behind in terms of understanding better vaccines and medications, how they work in pregnancy, how they can prevent these diseases, and how they can be best used in this population.

Alisha Wainwright 08:51

And so, uh, where are we at now? Is it fairly commonplace to have pregnant women and people in vaccine trials?

Flor Muñoz 09:00

Well, it has been a gradual evolution, right? And so there hadn't been vaccines that were developed exclusively for pregnant people. But we were doing some research - small studies - to demonstrate, for example, that existing vaccines - such as whooping cough vaccine - could be given to pregnant people safely and that it actually would result in antibodies that then pass to the baby and the baby would be protected. And that has been very successful. But that was a vaccine that was available for everybody - we just needed a little bit of information to be able to really recommend it and use it in pregnancy.

What has also changed though, is that with this knowledge, there are now vaccines that are being developed exclusively to be given to pregnant people, so that their babies would be protected. That is the case of RSV - or respiratory syncytial virus - which is the disease that affects babies at a very young age. All infants could be at risk, and yet there is no vaccine for babies, there's no treatment for babies, and there's no other way to prevent it than to give this passive immunity - so antibodies that come from the mother - and we can boost those antibodies in the mother through vaccination. So now, you know, research is happening so that we can have actually vaccines that are designed specifically for pregnant people.

Alisha Wainwright 10:16

So what extra considerations are there in involving pregnant women and people in vaccine trials?

Flor Muñoz 10:23

There is a path that has to be followed because, certainly, there has to be information collected before we can do research of a new vaccine in a pregnant person. So, for example, there are what we call preclinical studies - so studies that are done not in humans - so that is one step. But once you start going into clinical trials - meaning testing the vaccines in people - then you have to have some data in non-pregnant adults - ideally women of reproductive age - showing that the vaccine is safe and that the vaccine is able to produce the protection that you expect.

And once you have that information - for the most part - if you do have, then again, a disease for which pregnant women or their babies could benefit from this vaccination, then you could consider doing the clinical trial in pregnant people.

Alisha Wainwright 11:19

How do you make sure a vaccine trial is actually safe for a pregnant person to take part in? For example, what are safety signals - maybe you can explain that.

Flor Muñoz 11:29

A safety signal could be any type of symptom - usually - that some participant in the clinical study could report back to the investigator. It doesn't necessarily mean that it is caused by a vaccine or that it is even associated with a vaccine. But we do collect every information that we have regarding any symptoms that could or could not be associated with the vaccine after the administration. We would then tally and compare how frequently each of these symptoms occur in the vaccinated group versus the non-vaccinated group.

Alisha Wainwright 12:12

And how are they utilised?

Flor Muñoz 12:14

So, for example, fever - fever is not something that you would want to experience during pregnancy - especially in the very early phases of pregnancy - because fever results in inflammation and in certain changes in our body that could potentially affect the foetus. And so, one safety signal that you want to make sure you understand is how much fever you can have from a vaccination. So ideally, for example, vaccines that we want to use in pregnant women or do research for pregnant women to be able to use them, would have to have a very low risk for fever. That's just one example.

Alisha Wainwright 12:52

Yeah, that's a good example. Um, I just never really thought about the, like, layered efficacy, so that really - cause I'm just purely thinking of my own personal perspective. Like, if I was pregnant, would I want to do a trial and if it was really explained to me as you did - that it has gone through layered levels of trials and efficacy and there aren't these signals that would be benchmarks that I would be - should be concerned about as a pregnant mother - that would entice me to want to participate in something like a phase three trial. So, I think that, um, even just as an outside person who is not participating in a vaccine trial like this, it gives me comfort knowing that I hope these mothers feel like they're in a very safe and reliable, you know, trial.

Flor Muñoz 13:45

Well, that is what has changed, you know, because of the concept of inclusion of pregnant women in research as opposed to exclusion, which is what we do in the early phases. We really still do have to exclude pregnant women from the early clinical …

Alisha Wainwright 14:01

And I think that’s fair.

Flor Muñoz 14:03

Yes. Yeah. Of course it's fair, right?

Alisha Wainwright 14:05

Of course.

Flor Muñoz 14:05

And so indeed, um, there has been a lot of change in the last two decades because we have appreciated the benefit, as I mentioned,

Alisha Wainwright 14:12

Right.

Flor Muñoz 14:12

You know, we introduced, you know, the whooping cough vaccine after the flu pandemic in 2009. You know, there was a lot more interest, of course, in continuing to use flu vaccines in pregnancy, globally. And then RSV has been work that has been going on for decades. We know about RSV since the 1960s, and it has been a seasonal annual outbreak, you know, in Northern and Southern hemisphere - so a global outbreak that happen every year - that are, you know, really affecting a very, very large number of babies that - I'm telling you, as a paediatric infectious disease doctor - we have our hospitals full of babies with respiratory viruses during our winter season, and that happens globally.

So having the potential to protect them very early in life when they're most susceptible, with a very targeted approach - like a maternal vaccination - is actually really groundbreaking - and we are in a situation where people are understanding that, and this is why, say, uh, 20 years ago, it was very difficult - it took months to enrol, I don't know, 30, 40, 50 women in a clinical study - and now we're talking about tens of thousands of women participating in these clinical trials throughout the world because of the understanding of, not just the disease and the potential benefits, but also the process, right?

So, I think you're absolutely right - knowing how things are done - because it's all very carefully done. Obviously, there are a lot of players - there's not just regulatory pathways and discussions - but, you know, as I mentioned, that technology and the vaccines are made much safer right now. There is a lot of clinical work that occurs - so a lot of safe environments where you can do these clinical trials, and there's a lot of accountability as well, right? So we, as an investigator, you have very important responsibility to be able to work together with a mother so that they make an informed decision about being part of a clinical study.

Julia Gillard 16:16

Hello! I'm Julia Gillard, chair of Wellcome. Thanks for listening to our podcast, When Science Finds a Way. Wellcome supports researchers around the world to make discoveries and help solve urgent health challenges. We believe in the power of science to build a healthier future, and the need for inclusive collaborative action to ensure that everyone can benefit. To get involved, visit wellcome.org, that's Wellcome with two l's. Now, back to the story.

Alisha Wainwright 16:49

Okay, well, let's travel, now, to South Africa to hear more about this from Clare Cutland, Scientific Coordinator of the African Leadership in Vaccinology Expertise - or ALIVE unit - at the Wits Health Consortium at Wits University in Johannesburg. The Wits team has been running vaccine trials with pregnant women in South Africa and various other nations across the continent since 2010 - including the RSV trial you mentioned.

RSV is a common respiratory infection that can lead to fatal complications in newborn infants. There have been multiple attempts to develop a vaccine for it, and this one was created by Pfizer. Its phase three clinical trial is a multi-country project called MATISSE, and

the vaccine has now been approved for use in pregnancy in the U.S. and Europe, and is under review for use in several African countries too.

(music, into)

Here's Clare to tell us more about working with participants in pregnancy and the MATISSE trial.

Clare Cutland 17:52

There's extensive work being done in South Africa related to maternal health and maternal vaccination. Pregnant women are considered as at risk or special populations in any sort of clinical vaccine trial and cognisance needs to be taken of that fact that they may be at high risk for various illnesses related to the pregnancy. And they also need to involve their family, their group, their spouse, husband, partner, in many of the decision making. Because the decision that the pregnant woman makes is for herself as well as for her unborn baby.

So the participants in the MATISSE trial were enrolled across 18 countries, including South Africa and The Gambia in Africa. And they were approached - usually at the antenatal care facilities - where they were approached by clinical trial staff and they were informed about the trial that was happening. At the time there was no RSV vaccine licensed or registered for pregnant women globally - or anybody globally, actually - and the women were invited to participate in this trial, knowing that the phase one and two trials have already established safety in non-pregnant participants.

There were over 7,000 pregnant women who were enrolled in this randomised control phase three trial, and the results of that phase three trial were very, very encouraging - with more than 80 percent efficacy in reducing medically attended respiratory syncytial disease in the young infants up to three months of age.

One of the biggest challenges that took place in the MATISSE trial, is that the enrolment and a lot of the follow up happened during the COVID pandemic. And one of the adverse events that was identified in some of the interim and secondary analyses, was that in some areas - particularly in the South African cohort - there were slightly more preterm deliveries in the women who had received the vaccine compared to women who received the placebo. The vast majority of those preterm deliveries took place very late preterm - so 35, 36 weeks - and most of them actually overlapped with the various COVID 19 waves. One of the things to note is that even though there was a slight increase in preterm births, there was no impact on the survival or the health of the babies after their preterm births.

Biologically, it's not been ascertained as to why this adverse event would happen. It is concerning, and there's additional work that is being undertaken - specifically a phase four vaccine trial - which will be conducted across multiple African countries.

(music, into)

Alisha Wainwright 21:05

Wow. So, this is a complex topic, isn't it? As we heard in this trial, there are follow ups needed in South Africa because of the questions of preterm births, even though it's unlikely it was related to the vaccine.

Phase four trials usually look at the side effects caused over time by a new treatment after it's been approved and is on the market. And as Clare explained, the Wits team is planning to conduct one once the RSV vaccine has been approved for use by local regulators. This is so they can continue to closely monitor any possible adverse outcomes from its use, including preterm births.

I know you're part of the Independent Safety Monitoring Committee, who is overseeing safety for the whole RSV program. And I guess this is a good example of those safety signals we spoke about working and how much safety is always at kind of the front of everyone's mind in these trials.

Flor Muñoz 22:00

That is correct. Safety is paramount. I think that whenever we, as investigators or participants in the clinical trial, really consider being part of a trial, the first question that comes to mind is, is it safe? Is it safe for me? Is it safe for my baby? This is the reason we want to do the clinical studies because we want to be able to understand - as we mentioned - how to address some of these potential safety signals - especially in the case of this vaccine, where you have such high efficacy. So have a very, very high protection…

Alisha Wainwright 22:34

80% is great. Yeah

Flor Muñoz 22:36

Absolutely - high protection, like any other, you know, paediatric vaccines really, where babies are very likely to not have severe disease if the mother receives the vaccine.

So, despite this signal - this potential signal - you know, the vaccine is approved, as we have mentioned. But I think this is a good example of why it is important to do the clinical trials, because that was detected during the conduct of the trial, and it has allowed for this phase four clinical trial to be set up - which is again, trying to continue to see in a larger population if there's any relationship.

Because to be honest, this was seen in the middle of the COVID pandemic when there were potentially so many other factors that were affecting, you know, this outcome. And at the same time, even though there was a difference within the trial, the rates of preterm birth in that MATISSE study were below the background rate - so what you would normally expect to see in terms of preterm birth in the different sites where the study was done. And I'll just mention that there is a commitment from everybody that is involved in these clinical trials - from the vaccine maker to the investigators to the, you know, regulatory and recommending bodies like, you know, the CDC or, you know, other different groups, WHO etc - to continue to assess how safe these vaccines are - even after they've been approved and licensed. And it is our commitment to be able to stop using a vaccine if there's a concern.

I'll say this system works - we have seen it in the past. You probably have heard of, you know, rotavirus - which is a diarrhoea illness disease - that in the late nineties, there was a vaccine that was associated with a high risk of this intussusception - which is, you know,

some strangling of the gut - that is associated also with the disease itself. But you know, we had a vaccine that was very effective - it was being used - and this particular post authorisation safety surveillance system was able to detect that indeed, you know, this vaccine was associated with a little bit higher risk of that outcome. And so, it was discontinued - we stopped using it. And this is done for every vaccine out there.

Alisha Wainwright 24:59

Yeah.
Let's hear now from someone who took part in the MATISSE RSV trial. Thandiwe Nkosi was 30 weeks pregnant with her daughter when she was vaccinated as part of the study at the Chris Hani Baragwanath Academic Hospital, also known as Bara. We visited her - and her kids and pets - at her home in a township just outside of Johannesburg to hear what the experience was like.

Thandiwe Nkosi 25:29

My name is Thandiwe Nkosi. I am 34 years old. Before at the clinic when they introduced me or they told me about it, they didn't give me much information about it - they just told me that this is a study, but if you're interested you can go to Bara Hospital. But when I got there, they tell me what they are researching about and then that's when I got interested about it. They told me they're doing research about pregnant women and the baby. They explained to me that the vaccine is gonna protect the child from getting infected with the cold because normally the kids are so vulnerable.

I had to think about it first before going there because, uh, you know, sometimes you feel sceptical - you can't just hear about something and then you just go - you think about maybe the consequences or the effects after that. But trusting that Bara is a big hospital - I don't think they will put my health at risk or my child's health at risk - that's when I was like, let me go for it and see how it goes, yeah.

My partner was a little bit concerned about it thinking maybe it will affect the baby in some kind of ways. But then I was like, no, those people are the expert - before they give you the vaccine, they need to check your health - if you're a hundred percent healthy. They told us everything about what we're going through or what we are doing with the study. Because the lady that I was dealing with directly, she used to explain to us most of the things that we're supposed to do. Any questions that we had, we had to go and ask her. So I think we're well informed about it, yes.

After the vaccine, I didn't feel any different in my body. That's what I can say. I didn't react or get sick after that. I didn't get anything. So I was fine after - even after taking the vaccine. We also had the diary that we filled in every day to check if you are doing well and the baby is doing fine. If there's anything - maybe you're not feeling well - you write it down or report to say, I'm not feeling well - then they can check up on you.

Even after the baby is born, then you still keep on updating the diary. They will also call me to ask me if I'm fine and if the baby is fine. And if there was anything, then I would call them and say I'm not feeling well or if there's something wrong. But I didn't - I didn't have any problems after that. But they will keep on checking up on you to see if you're one hundred percent okay. I think she was around one-year, six-months - that's when it stopped.

If you are going to a clinic, normally the clinics are not paying much attention to the - especially the public ones that we're going to - they don't do the thorough checkups of the baby. So if you take part in the research, they were able to check your it's growing well, or if there's abnormalities in your babies - then that's when you're going to be able to find out or know in time. Definitely, I will do it again. I will even recommend somebody if anyone is pregnant to say, if you want your pregnancy to be easy, you go through this process. It was easy for me. I was happy.

Alisha Wainwright 28:57

I love Thandiwe's, like, jovial perspective on this. It's just such an easy, thoughtful experience in which she felt monitored, safe, in good hands, and she had no adverse effects. So really, she's kind of the poster child of a very positive experience. And it's interesting to hear about all the monitoring and follow ups with Thandiwe.

Um, is it usual in a trial, involving people who are pregnant, to have that many follow ups?

Flor Muñoz 29:29

It is, it is - again, because it's very carefully designed at clinical trials in pregnancy - very, very carefully designed - to have as much information as you can prior to being part of the study, in terms of ensuring the health of the mother, the health of the foetus, you know, understanding what gestational age they're in to give the vaccine at the right time. And then very close follow up afterwards - that again, is really trying to make sure that we don't miss anything. That diary that she mentioned is very important because that's how we know from the moment the vaccine is given until several days later - what happens. And, you know, we're not saying the vaccine is causing those symptoms - pregnancy itself can make you tired.

Alisha Wainwright 30:12

Right, yeah, of course.

Flor Muñoz 30:13

You know it can make you have body aches and so on. But this is why a group receives a vaccine and a group receives not the vaccine – you know, a placebo. And that's how we compare. And that's where we see if there's a difference or not.

But, you know, I agree with you. I think that our clinical trial participants are very special - and even more special when it comes to a pregnant mother coming into a study - because she is in a vulnerable situation in that she's caring for herself, for her health and for the infant. In addition to that, she mentioned so many important aspects of this - making sure you have the support of the partner, the mother, the mother-in-law, you know, the community - everybody around them is very important. And also, of course, of the physician - so having the trust in the clinicians who are doing the study, and the other members of the research team - is going to be very, very important.

She talked about being informed, you know - and this is again, very, very key - because it's not just understanding what is going to happen or the tests and the care that she's going to receive - and this is actually true - it's very true - that in many places the care you're

receiving under clinical study is more detailed and more thorough than you would in a normal clinical situation.

But certainly, I think that one of the aspects that we see in our clinical trial participants, is that they do feel important being part of something bigger.

Alisha Wainwright 31:46

…bigger.

Flor Muñoz 31:46

Being part of contributing. And they're doing this for themselves, but they also understand that eventually this is something that could help so many other women and their babies.

Alisha Wainwright 31:56

So in general, what are the barriers which can make it challenging for trials to take place in the U.S. where you work?

Flor Muñoz 32:03

Yes, I think that the challenges are related to acceptance of vaccine as a preventive strategy - you know, in the U.S. we do have more problems with acceptance than many other countries. Other countries, a population is more trusting of their health care providers and, you know, they will accept vaccination. That is a problem here. The willingness to be part of research - to be able to get informed and to be part of something different that requires your time and effort - is a barrier, you know, it's a challenge. Because it means I'm going to have to not go to work or I need to take my child from school or, you know, do things that are outside of my routine to be able to go to a clinic and spend several hours there doing the study procedures - even doing a diary, you know, sometimes just - it's - we do it electronically now.

Alisha Wainwright 32:51

It’s cumbersome - it can take time. Yeah.

Flor Muñoz 32:53

It can take time.

Alisha Wainwright 32:54

It can get away from you too, if you have a busy life.

Flor Muñoz 32:56

Right. But, but I think that the main issue is, you know, to have the proper research team that understands what they're doing and that is able to establish that trusting relationship with participants, and that, you know, you're able to really have good communication and comply with all of the requirements to do a good clinical trial.

Alisha Wainwright 33:18

Interestingly, Clare Cutland told us that recruitment hasn't been an issue in the countries where Wits work because the prevalence of disease is so much higher, so people are more aware of the risk of not receiving treatments.

(music, into)

But Clare did tell us about some of the challenges they do face.

Clare Cutland 33:35

Conducting clinical trials is fun and challenging, all at the same time. So, some of the challenges that we have experienced in conducting trials in low- and middle-income country settings - that are maybe not as obvious in other high income country settings - are the availability of routine healthcare. For example, the access to ultrasounds has been a challenge in many other countries.

For what has had to be done across many maternal immunisation trials, is that the trial has had to be able to train, for example, sonographers, and provide sonar machines to ensure that the gestational age and congenital anomalies, could be assessed accurately. Other challenges include the fact that many women - in particularly in low- and middle-income country settings - use injectable progesterone containing contraceptives, and these can significantly impact the regularity of menstrual cycle, which means that utilising the last normal menstrual period to assess gestational age, is often quite inaccurate.

In many countries - but particularly in low middle income countries - many of our pregnant women are exposed to other infectious diseases - so malaria is one of the infectious diseases that can significantly impact the health of the mother, the unborn foetus, and the newborn baby and can reduce the transfer of antibodies across the placenta.

So we have seen that, as an example in South Africa, we've got a very high HIV positivity rate in pregnant women, with almost 30 percent of pregnant women having been infected with HIV. In South Africa and in several other countries, the access to antiretrovirals is good, but in some particularly low income country settings, access to routine care - for example, antiretroviral treatment - is limited and therefore viral reduction in the HIV positive mums is often not good.

(Music, into)

Alisha Wainwright 35:57

There are so many health inequities which feed into this, aren't there? It's interesting to hear about the intersection between pregnancy and other infectious diseases and just - stuff like

basic access to prenatal care - so varied in different settings. How do you think including people like pregnant women in trials can make health more equitable?

Flor Muñoz 36:17

Yes, I think that that is also something that we need to work on. There are different types of inequities - we see it everywhere - we see it even in resource rich countries. Another one is education, you know - so being able to have access to the information and having access to people that you can talk to and trust to make decisions, is also important.

We saw probably some of the biggest inequities during the COVID pandemic in terms of just access - just being able to even have the vaccines available in countries that needed it. But I think that doing research is one way to be able to increase the opportunity for some groups who normally would not be able to have this type of level of care - to receive good antenatal care, to receive good perinatal care, and even follow up of their babies.

And it should not be the reason people participate in the clinical trials. But I think that through research we could potentially improve the conditions of antenatal care and perinatal care in countries that have been able to set up sites for clinical trials. I do believe that places that are able to set up some of these research units and have now set a new standard for their care and for the population, are a good start to be able to disseminate this out.

Alisha Wainwright 37:52

So, what more needs to happen globally to ensure more vaccine trials - or other medical research in general - can take place involving pregnant women and people?

Flor Muñoz 38:05

Yes, there's a lot of work actually happening already. Part of it is having specific guidance on how to do research in pregnant women. That exists in many countries. There are actually international guidance documents that are available. We have also had advocacy groups. And clearly, I think that, you know, the resources are always important, right?

Alisha Wainwright 38:29

Yeah, of course.

Flor Muñoz 38:30

The resources - financial resources, and also the physical resources to have teams that are knowledgeable; to have ethics and regulatory review committees that are comfortable to, you know, allow these studies to happen; to have the financial support from large investors - so to speak - you know, that are willing to take a risk, if you will - you know - to be able to study the vaccines in pregnancy. Because I think, you know, now that the doors are open in terms of acceptance of maternal immunisation as a strategy for disease prevention - that is not just individual, but it's a public health intervention where many other examples are being considered - the question that people should be asking is why not including pregnant women? And it needs to be justified. Now, why we are excluding pregnant women from a potentially very beneficial vaccine or medication for that matter, or an intervention, you know.

So, they are a vulnerable population - although we don't like to use that word because they're not vulnerable in the sense that they're, they're fragile and unable to make decisions - this is a regulatory ethics term, you know - and all it means - it has nothing to do with a person being vulnerable - it has to do with the implementation of additional safety measures.

Alisha Wainwright 39:52

Extra considerations - yes.

Flor Muñoz 39:53

Extra considerations that are actually applied - because we're talking about a mother and her foetus and her newborn, that could be affected or not - you know, positively or not - by a particular intervention. And so, extra care, extra attention, specifically designed products like vaccines and drugs, specifically designed trials and follow up studies, safety monitoring - needs to be done for these populations.

Alisha Wainwright 40:20

Wow. Well, you said it. I think the main takeaway that I'm really gathering, from what you're saying, as a 'What do we do next and why is this work so important?', is not just to assume the exclusion of pregnant women and people, but to ask 'Why? - why would we exclude them and is that necessary?' Because we could be doing more of a public service by including them in a safe and effective way in which everyone understands what's going on and everyone feels safe moving forward. I think that that's fantastic. And the work that you do is so incredible. Thank you, Flor, so much for joining us today. I really appreciate your thoughts and education.

Flor Muñoz 40:59

Thank you so much and I think we are at the beginning of a new era. If I may just say as a last word - we've come a long way in the last two or three decades, and we are about to see more, about the impact that maternal vaccination can have in these diseases for which we have vaccines already, but also for the potential for impacting other diseases. So, I think the future is very bright and I think that we need to be positive and optimistic of the fact that we have the right tools to be able to move forward with maternal vaccines.

(Music starts)

Alisha Wainwright 41:36

Thanks for listening to When Science Finds a Way. Thanks also to Flor Muñoz, Clare Cutland and Thandiwe Nkosi.

Thinking on our conversation - it's definitely complicated. And let's be clear - there's been far more progress in maternal vaccines than many other areas of vaccine or drug development. But, there is still a long way to go. But the level of assuredness and sense of safety and peace of mind that I have for these mothers participating in vaccine trials and the health of their foetuses, I think it's really important that we understand Flor's takeaway sentiment - which is to ask why not include them? So, forcing ourselves to ask that question as you go through the process, I think, is making a better healthcare system.

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If you've been enjoying When Science Finds a Way, be sure to rate and review us in your podcast app. You can also tell us what you think on social media - just tag at Wellcome Trust - with two L's - to join the conversation. Next time we'll be talking about new ways to track and stop the spread of cholera.

Iruka Okeke CLIP 43:29 - *"If you think about the fact that every cholera case is somebody who's eating or drinking Vibrio cholerae falling sick - if you can just prevent one person eating and drinking cholera, you saved more than one person."*

Alisha Wainwright 43:42

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(Music Ends)