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TRANSCRIPT - GR 01 13 23 "Update on Malaria Management in the U.S. and a Review of Novel Antimalarial Therapies" Johanna Daily, MD MS, from the Albert Einstein College of Medicine

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- So yeah, I think I'm gonna get started. I think everyone out there can hear me on zoom, and people can hear me in the room so welcome to medicine. Grand Rounds Day. I'm. Excited to present Joanna daily Dr. Joanna daily.
- She's a professor of medicine and infectious disease, microbiology, and immunology, and Albert Einstein College of Medicine.
- She has an exciting talk prepared to us today about advances in malaria treatment. Before I go any further today, though, I do want to make one announcement to the attendees in the room and on Zoom. Just remember that it is the beginning of the 30 year clerk ships on the seventeenth.
- So please play nicely, and that's to the residents as well.
- And then also I plug this maybe once or twice before, and I put a link in the chat for those of you who are on. Zoom. Please consider giving to the Against Malaria foundation. This is a Uk based nonprofit, dedicated to providing long, lasting insecticide, treated mosquito nets
- for populations at high risk of malaria. Great. So okay, but now back to Dr. Daily Dr. Daily completed her Residency training at the New England Medical Center in Boston, followed by a clinical fellowship at the Longwood Infectious disease program, and finally a Research Fellowship at Harvard School of Public Health.
- She then began her Academic faculty career at Harvard Medical School, working at both Brigham and Women's Hospital, and as well at Dana Farber
- in 2,009. Tired of the small city that is Boston, she moved to the Bronx and began her career at Monte Fiore Hospital, where she continued to excel as a researcher and educator of the finest rank.
- Dr. Davies's primary research focus is the biology, pathogenesis and immunology of plasmodium Feliprum.
- The goal of her research has been to define the molecular mechanisms that underline the stark variation in presentation from asymptomatic to cerebral coma Our cerebral edema, coma and death.
- and ultimately to identify parasite and host processes which can serve as targets for vaccine or chemotherapeutic development. So please put your hands together for Dr. Joanna daily.

Johanna Daily

00:16:22

Thank you very much, Kevin. Thank you for invitation to talk about my absolutely favorite topic.

- and I do have the chat open, and i'm hoping to get some good questions and discussion.
- So
- today I'm going to review really the latest update on malaria management, who released
- their recent guidelines, November 2,002. I want to review that.
- and then I want to talk a little bit about the status of the vaccine and monoclonal antibodies.
- So our learning objectives are really update on management of malaria.

- and knowing about some of these anti-malarial therapies coming down the pipe.
- So I have a whole bunch of cases, and i'll start with case one. This is a 44 year old female patient who presents to the emergency room with complaints of fatigue.
- discomfort.
- chills, loss of appetite and subjective fever. For 4 to 5 days.
- She was born in Guinea, and migrated to us approximately 10 years ago. She traveled to you need for one month visit, and presents after 5 days after returning to the Us. And did not take any purple access.
- and I I always like for my medical students to look at these, and then really pick out the key features, and I think the key features here
- or
- this very non-specific syndrome, and that's Why, malaria is misdiagnosed. In our own review, 43% of the time in children and 23% of the time in adults here in the Bronx. So they were misdiagnosed before they were ultimately
- admitted, and children at a 43% rate they tend to have more diary and abandoned symptoms and that's the problem with malaria. It's a very non specific syndrome, so none of this is going to help us. This is typical malaria, but of many other illnesses. But here's our smoking gun clues that she visited Guinea.
- and for most of our patients with malar in the Us. They are visiting friends and relatives, and they are not taking purple access.
- So here is this is a real case: blood pressure, stable. She's tachycardic, febrile, oxygenating well, and typically they have a non focal exam, but I want to point out sometimes they have pulmonary findings, and that puts you down it to a pneumonia route or abdominal findings. So try not to be misled.
- for the exam is on focal.
- They often have elevated, create need and kidney diseases being more and more recognized, particularly in severe malaria.
- Generally there are, we know, function returns to normal, except in the case, of course, of malaria, which can go on to develop. Familiar to this Reno failure.
- the white count just to help us. It can be low. It can be normal or it can be elevated.
- I think the smoking guns are definitely. They're going to be anemic. This parasite resides in red cells, resulting in a red cell loss and absolutely from a cytopenia.
- I would start to doubt the diagnosis. This is probably an itp mediated phenomena, but you almost always see from the cytopenia in malaria.
- So in this case she had a positive or dt and a positive confirmation on blood smear.
- So this is the latest data from the Cdc. It tends to be old and hopefully they'll improve that.
- We see about 2,000 cases a year in return on travelers to the United States. Virginia had 66 and 2,000, and 18 perhaps that was all belt way malaria.
- and most of them are in our patients visiting friends and relatives, and I think malaria, of course, goes up on the list when i'm seeing a immigrant returning from a visit home
- occasionally. They're cryptic cases. We do have typically 2, 300 severe malaria cases and always a handful of deaths every year.
- You know most of the world's malaria is also from hundreds of millions of cases. So is the most prevalent malaria. Ivax comes in at number 2, with about 2 million infections a year Again, returning travelers often aren't taking chemo purple access. However, if a patient says
- I took my prophylaxis, they can still have malaria. I think that diagnosis goes down on the list, but it's not a 100%, and often patients take their malaria prophylaxis, but they stop upon returning to the Us. And they don't complete that, too.
- So I would just get a smear to everybody that I'm concerned about malaria.

- and about 85% of cases are required in Africa. That's where it is most hyper endemic. That's where many of our patients are visiting. But Africa malaria is still prevalent. About 40% of the world's geographic locations.
- The diagnostic approach remains old-fashioned, then in thick sneers.
- I would absolutely order them to allow speciation
- 6 or 20 times more sensitive than fins, and they're much more sensitive than Rdts. Probably a thin and an Rdt. Have equivalent sensitivity.
- Picks are more sensitive. They take a lot longer to get the result, because we need to lic the cells and dry, and that takes an overnight. Typically.
- people should be looking at many fields, spending at least 20 min.
- and to roll it out we need 3 smears.
- Rarely is it smear negative. I've never seen this in 2030 years, except. I finally saw a case at the Bronx, where the admissions here was negative. We did go back and look at it was negative, and later became positive. So if they come in with the negative sneer.
- my suspicion is going way down. However, if they are very ill.
- totally reasonable to start empirical therapy. But you should be able to make the diagnosis. This is not a mysterious diagnosis.
- and I think if that first smears negative start to think about things like typhoid or sepsis, or other, maybe orbital viruses.
- The modern
- innovation, of course, is rapid diagnostic tests. These are rapid. We don't need expertise.
- and there's. One FDA approved test called my next. Now FDA requires that we confirm both a positive and a negative test.

Unknown Speaker

00:22:44

Rdts. Do not quantify infection.

Johanna Daily

00:22:47

They will not detect that fifth human malaria. No, I

- and they're really not sensitive for the non-fel different species malaria or valet
- and vibe. And the reason is these other infections. Parasitemia tends to be less than 2%.
- So if you get a positive R Dt. Fabulous. But if it's negative, still it's still a possibility.
- And we're going to at that point. Wait within and fix me.
- Microscopy is absolutely the gold standard
- problem. As many hospitals. Don't have parasitology expertise, so you may have to rely on your pathologist.
- I do occasionally look at malpractice cases. One mal practice would be saying, Well, let's wait till tomorrow to determine if this patient has malaria. Can't really do that.
- I think our Id folks can look at the smears as well, and Felip Room has typical features, high parasitemia. Only the early stages are seen in the blood. Later stages sequester

- my backs, prefers particular sites. So you see them infecting these large red cells. You see sh ship ner's dots. You see how a meat boy they are. I don't think any of us will confuse these 2,
- of course, where they originated, where they acquired malaria is going to help you sort of guess which species, although many areas have overlap
- the other. Much more rare species or valet red cells all shape malaria, staff forms, and knows the I which
- we hardly see the United States. There is one case in 18,
- but the truth is that all these species have ring stages, so it's possible that you're looking at rings. You don't have the smoking gun textbook images.
- if you're not sure if it could be, and they're from a drug resistant area.
- Artemis and accommodation Therapy works for every species. The reason we don't use it for the other species is chloroquine works. It's less expensive, and you're going to minimize drug selection. So that's just a pearl to know we're not absolutely sure we can use act to treat
- malaria. If you don't know the species.
- every single case of house of room we review severe disease, criteria, and this is another error. I see sometimes in cases that
- malpractice is in play.
- So we kind of go through the laundry list of any of these clinical manifestations.
- and because malaria can be so tricky, maybe you don't have any of these. You have some laboratory tests that point out. This patient has severe malaria, so
- we we always go through this on Every patient
- generally fell from but 5 acts can also cause severe disease.
- So for our first case, he buy back overnight. Her blood pressure decreases to 70 over 50, and she's unable to take Po
- and I've seen this in at least 2 cases where the patient comes in beautiful notes written they have, how they are prom, and they defend. Why, it's not severe malaria and Ib. Therapy is not needed, and then the patient deteriorates. So
- I think, as a consultant I need to put that in every note that please F. Right now. The patient has mild malaria, but really follow them closely, and if they deteriorate and develop any severe disease criteria.
- Let's get Idr testinate and let's get close observation.
- so that that that's one major point, or I wanted to make today.
- Our testimony is now commercially available. Prior to about 6 months ago we had to ring up the Cdc. They would fly it into your local airport, and you would go out and pick up our tests in a
- Finally, it's now commercially available.
- and at least in New York. We do stock it.
- 3 doses is about $30,000, so we share it among New York City Hospital, so we can rapidly get it.
- Whether University of Virginia should stock it, I don't know, but they should have this phone number ready to go.
- If for some reason you cannot acquire it from the commercial source.
- Cdc. Will supply you if you can't get it within 24 h, but they want you to first
- go and try to get it on your own.
- What do we do? In the Meantime we don't really have I
- quinine?
- We can go ahead and give oral therapy. So act is the way to go Artemis and Accommodation therapy as compared to Mallorone or the other drugs is most rapidly acting.
- and for the Id fellows and anyone who manages these patients
- after our testinate there's a risk for Homolysis post therapy. So every week for 4 weeks after I complete my artes and a therapy, I have the patient

- do a hematocrite, and if I start to see a large drop in the Madrid
- that is post-war test and a homolysis, and maybe I have to transfuse them. So that's the thing to keep in mind if we're using our tests in a
- to follow for post or testinate homologous for 4 weeks.
- Question for the audience. How do I manage your first trimester pregnant women with Helsip from malaria.

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  00:28:03

  I'll feel any answers here from the audience.

- but I'm protected from having to answer myself. I think

  Johanna Daily

  00:28:12

  good strategy.

- I'll be impressed if anyone gets this right, because just changes recommendation. In November

  UVA Medicine Grand Rounds

  00:28:26

  Mephoquin.

  Johanna Daily

  00:28:28

  Methylquine is not a bad answer

- all

  UVA Medicine Grand Rounds

  00:28:31

  but it doesn't sound like it's the right answer.

  Johanna Daily

  00:28:34

I'm not against it.

- What are the other possible drugs? And I like that? You're remembering that she's from Guinea, and how soprom is going to be chloroquine, resistant, so cork would be absolutely not. Methylquine is the therapy for drug resistant malaria.
- What other drugs could we use? That might be more gentle and frequent, often causes gi symptoms

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00:29:05

there again.

- Oh, no, I couldn't understand in the back. I just don't know my drugs well enough. I think
- Valer down at Tova Kone.

Johanna Daily

00:29:14

Okay, good thanks for some answers. So that's great. So, Mallory, it's still contradicated in pregnancy. It's a to phone for. Want to. But I like that You're staying away from for Quinn

- prior to November. 20 s, 2,002.
- We were staying away from Artemis, and in combination therapy, and I think the audience was as well. So we were supposed to give y 9 plus quinda to our pregnant women, because there was a concern that Artemis, and in first Trimester may cause some neonatal abnormalities.
- So now there's a lot of data that actually it's safe in first trimester. So the new recommendation is.
- I can give Artemis, and in combination therapy
- for any patient with drug resistance felt so from whether they're pregnant or not.
- So prior to November it was my 9
- and Linda.
- But now we can go ahead and give Artemis, and in combination therapy
- to our first trimester. Pregnant women
- look. If only Methyl quid is in the pharmacy, I would definitely use meploquin so that that's a that's a fine answer. And really we have to use what's in our pharmacy we can't withhold therapy.
- So let's see if.

Unknown Speaker

00:30:25

because

Johanna Daily

00:30:27

just having a little problem moving, my

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00:30:29

sometimes, I might have to click you back onto the screen. Oh, Yes.

- Does it work now?

Johanna Daily

00:30:36

No.

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00:30:38

huh?

- Let's look. Try one more thing here.
- I'm going to remove your I'm: going to make host.
- Yes.
- and try it. Now.

Johanna Daily

00:30:54

Okay, very good. So this is the new recommendation. We can now come in with our to be put in the Phantom, which is the act we have the United States in any trimester.

- But, as the audience said, look what's local, if it's Methyl Quinn great if we have quinine. And that was the old fashioned way. We can still go with that
- after delivery. We're gonna let the pediatrician know there's a possibility that there's neonatal malaria. It's very rarely transmitted to the baby, so I will let the pediatrician know.
- and we're good to go. So that's one updated

Unknown Speaker

00:31:31

fact.

Johanna Daily

00:31:31

All right. Let's move on to a different species. So this is case 2. This is a 40 year old patient, presenting with fever chills, body, externalized weakness and multiple joint pain

- for 3 days in Mumbai, India.
- where we know both fell super and vivac coexist, physical exam, febrile
- blood pressure.
- little bit low, 80 over 60 nonfocal exam. Again we see anemia normal white count. We see those low platelets
- or Dt. Was seen or positive by R. Dt. P. Bybacks from by a smear in our tests andate was initiated for the hypertension. There was a concern about severe disease.
- and this is a true case. Report next day became hypertensive, developed pulmonary Dema, and was intubated.
- and the reason I wanted to present this case is, we generally think of P. Byvax as benign. It's not fact. It's considered one of the benign malaria's, but there's more and more data, but that is not the case. As a matter of fact, I think, in 2,016 we have the 6 deaths in the United States. We're by back.
- So it's becoming increasingly recognized that vivac can cause severe disease.
- and there's some really interesting new papers that
- there is this extra vascular burden of vibeax in the spleen of all places?
- Now, you might say, Well, wait a minute. The spleen is where we clear, infected red cells. There should be parasites there, I agree, but they're finding viable collections of power sites in the spleen.
- In addition, there seems to be a higher burden in the bone marrow. So, even though our purple smears are 2% or less.
- it's probably a much higher biomass.
- and that probably could be measured by looking at one of the parasite proteins to to be rich protein to which you can test for buybacks as well.
- So I just want to highlight that vivac.
- We need to have respect for it. It can cause severe disease.
- So the patient recovers was treated with articulate. By the way you give or testinate for about 3 doses. If they're less than 1%,
- we then complete a full course of anti-malarials. So for our first case, she got our test in a. Then she got 3 days of act. In this case our testinate less than 1%, and then we complete the course with Corp.
- But as we all know, O Ovali and Vivacs patients have a prolonged liver stage.
- So my next question is, how are we going to manage the Hypnosoite stage of P. By X.
- Are you going to treat that stage?

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00:34:14

What anything

- prem equipment we got printed from the back

Johanna Daily

00:34:21

Wonderful

- So a great option
- because we're remembering that standard anti-marials don't
- kill this prolonged liver stage. It has a different biology, These drug targets are not there during the liver stage.
- but we have 8 amino acids, and permanent is one.
- So Premiquin was investigated as a anti malarial for blood Stage malaria didn't work very well, but they noticed wow patients with bybacks didn't seem to relapse.
- so they approved it
- for radical cure and radical cure means
- I've cured the bloodstream patients feeling great.
- but I need to radically cure the liver stage, otherwise they will relax.
- So that's called a radical cure. It also kills gamutocytes. So if you want to get rid of transmission in your community. You need to kill gameta sites. Chloroquine does not get rid of the Meu sites. So if you want to impact transmission, we're going to give it to Kilgameta sites, and it's actually a good preventative anti malarial.
- The big problem is, it's contradicted in G 6 Pd.
- We can't give it to children or pregnant moms. Now this is another November. 20 s update is that we usually give it for 2 weeks.
- but to be a show says we could give it for one week.
- The reason is, nobody
- can take Meds for 2 weeks. Maybe if we say to our patient, you only need to take it for one week. They'll actually do it
- slightly less effective, but it still will decrease the relapse rate
- to find a quin

Unknown Speaker

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was FDA approved in 18.

Johanna Daily

00:35:57

Everything is the same in terms of indications and adverse events. But here's a beautiful thing. It is a single dose.

- and so I think it's a major major breakthrough

- just to make things a little complicated. They're 2 different formulations that to Penn Aquin for 2 indications. So one indication is, I just cured my patient of active blood Stage 5 acts like our case 2, and now I want to cure them. So they don't have a relapse. I would give print to fill
- 2 tablets 300 milligrams times one.
- The other person i'd give Radical QR. To is my patient was a Peace Corps volunteer. They're in a P. By back and down the country. They've been taking chloroquine religiously.
- Problem, Ms: Glorquin doesn't clear
- the liver stage. So i'm going to do a radical cure to my person who's been deployed into a P. By back area so they could get Crinte.
- The other place you could use to fender coin is to prevent malaria, and in this case it's called Ourakota.
- and we'll talk about this a little more. You load. You only have to give it weekly, because it has such a long half-life, and then only a single dose post. Travel.
- Now, if you only have our coda and not Crin, if
- you could use that for radical cure. So we need 300 milligrams. You could give 3 tablets for the radical cure.
- Now. G 6 Pd. Deficiency is the Achilles heel of the amino acids, if you remember, G. 6 Pd. Is a very important enzyme to convert Nadp to nadph.
- which then is involved in good bye bye.
- our red cells are always under attack from reactive oxygen.
- If you have glut of my own, it scavenges our OS and your red cell membrane. Stay intact. If you have this deficiency.
- Anything that causes Ros. You're going to have Homolysis father Beans other drugs, and you mean open a lines.
- And the ironic thing is G 6 p deficiency actually protects against severe malaria. So a lot of the areas where malaria is endemic.
- there's actually a high prevalence of.
- So actually this is common they found in will endemic regions.
- If you remember it's encoded on the X chromosome. So males are more susceptible.
- but females can have sort of an intermediate level of function.
- So if you did a one qualitative test in a female, she looks like she has a intact enzyme. You give her primoquin. She can healize because the qualitative test
- cannot detect this intermediate level.
- So for
- women we need a quantitative test to capture this
- G 6 Pd. Is interesting, is over 186 mutations. So when you send a test is actually to functionally test the enzyme
- and all patients, the G 6 Pd. Testing prior to use of premiere. They need to have at least 30 of function in the enzyme
- or for Topenaquin greater than 70, and the reason there's a higher bar here is if I give to penguin and they healize. It has a very long half-life.
- whereas pom aquin, if they hemalize, I stop it right away, and the drug is out of the system.
- So the bottom line is, we need to do quantitative testing before we ever write a prescription for Primoquin or to Fenaquin.
- And when I think about malaria prophylaxis.
- I think about the frequency, and I talk with my patient.
- Are you good at taking pills every day. Would you rather take it weekly? And then I think, about what might be conjunication? So if someone was going to a drug resistant lerandemic site, these are our possibilities to find a Quinn

- tobacco and Malarone doxy cycling again. We're always loading people to get them a blood level
- in the endemic area. It's either going to be weekly or daily
- and then post travel.
- We need to give some therapy, because, remember, most of these drugs are working on blood stage malaria, and in the case of alcohol the liver is seeding the blood for 4 weeks. That's why we need a drug level for 4 weeks, unless the drug kills the liver stage.
- So, for example, prior to defend a when we'd probably give chloroquine to someone going to a p weive Xandemic area.
- It's a fabulous drug long, half-life, weekly. They would have to take it for 4 weeks, coming back, as the liver is releasing the
- memorialize.
- it will not prevent a liver stage relapse.
- So when they come back I have to give them a radical cure anyway, with permission. But now we have Tophedic, when
- so I would prefer to penetrate again. I'm going to load it for 3 days. Take it weekly in the endemic area, and again it's going to kill the parasite at the lumber stage.
- They only have to take one dose upon return. So I would say
- Defender Quinn is probably the drug of choice for patients going to P. By back endemic areas
- as long as they have a normal G. 6 Pd. They're not pregnant. They're not an adolescent, and they don't have psychiatric illness.
- A couple more fun questions.
- Can I treat a blood-stage malaria infection? Who's to fennequin
- anyone who want to treat bloodstage with Tophenne?

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00:41:16

I'm gonna go on a limb here, you know. They say, when they ask the medical students at 50 50 question, they get it wrong. Every time is what i'm going to feel like I'm going to say you can. Seems like a great drug

Johanna Daily

00:41:26

it is, but it's not really.

- I like it, though. See now, you're never going to forget this.
- So you know, it was like premiere when it was originally developed for blood stage. That's where people are dying and what we want to treat.
- and it didn't really work well, but they so they found that it prevented relapse.
- Same thing as to panic. When
- I think you're partially right, because there is some blood stage activity and give you half credit.
- It's not
- yes, exactly so. Actually their trials of to kind of quin and chloroquine ongoing.

- Now we talked about a pregnant woman with falseciprocal malaria. We said, we can now use acts in first trimester.
- What about my pregnant p bybacks malaria patient
- she's pregnant first, her second trimester. She's ill. She has buybacks on her blood, sneers

UVA Medicine Grand Rounds

00:42:26

I'm going to hand this one back over to the audience. Here.

- see what we got. I had some good answers from the back of the room, originally
- looking towards them.
- Oh.
- quinine and a zyth row.

Johanna Daily

00:42:45

So we have our quinity, and like our quinine and Glenda kind of mix. So I think that's an option.

- and you know most fly backs is still core sensitive
- for the Id fellows in Papua, New Guinea. It's not Papua New Guinea you have to use Act, but for everybody else.
- Ivax isn't very smart. It's still corporate still works.
- So I think the teaching point for me is, and I'm not against.
- By the way, if I don't have 4 quin, I like the answer. I like quinine. My now works against everything.
- but
- you could treat it a core one.
- Now the thing is, we can't give pregnant mom an amino quin a line, because it's not safe during development.
- So, and I've seen this mistake maintain, so treat her blood stage infection.
- but then maintain her on chloroquine every week until she delivers.
- remind the pediatrician that Mom had malaria, so they can check the baby.
- And now we have to give Mom a radical cure.
- If Mom has a normal G. 6 Pd.
- If she's breastfeeding, we have to document. Baby has a normal G. 6 Pd.
- So I think the teaching point here is.
- please prophylax, mom. I've seen that people, for they do this. They feel great. Mom feels great. They forget to do this, and then Mom relaxes.
- All right. I'm going to help you guys out with this Just nobody. I'll be surprised if anyone knows this. This is such a little
- tiny fact. Can I use Tophenic, when, after treating P. Backs with Act to provide a radical cure.
- so number one P. Box is generally sensitive to chloroquine, except Papua New Guinea. But if you gave act to treat P by back. That's completely reasonable to who says Laura Quinn, or act?
- I don't understand it, but it doesn't work

- to give to Pennines, so the answer is, Can I use to defend a qu if I cured my patient with act? No.
- So to Penn Aquain can only provide a radical cure if chloroquine was used.
- So in this case we'd use permission. By the way, that's just extra credit for the Id fellows.
- It's kind of interesting.
- Okay, one more quick
- case, and then we're going to move on. How do I manage my patient with G. 6 Pd. To deficiency
- and they have an untreated hip as a white infection.
- So I would say
- fundamentally, how often are people going to relapse? Actually, people relapse? There's some great studies where 30, 40, 50% will relapse in the next 12 months.
- So we really want to clear that hypnotized stage.
- My patient has G 6 Pd. Efficiency.
- What am I going to do with them?
- How would you guys counsel that person?
- What you can do is still use primoquin much lower dose 0 point 7, 5 min per kilogram every week, rather than every day for 8 weeks.
- and you can use Prevost and privoquent as an incredibly short half-life.
- So what you would do is
- say, we're going to give you proboquin. There's a small chance you might hemalize. So if your urine turns a certain caller, let me know. By the way, I'm going to check your hermatic word every week for 8 weeks. So this is one way to still eradicate the hypnosis. Away your patients with G 6 Pd. Deficiency
- in up today, and I think who supports this. You can also keep people on chloroquine, perhaps for 12 months afterwards, just so as was hitting the Zoites or entering the bloodstream. You're killing them when they enter the blood, but
- you could absolutely do this.
- Okay, so I'm just going to summarize some tophene. I think it's incredibly exciting. Instead of giving patient 2 weeks therapy when they feel fabulous, we're going to be single dose.
- It's due to its very long half-life.
- but it has the same problems as premiere. I can't give it in g 6 pd I can't give him pregnancy or lactation. I can't give it to a children under 16.
- So we need more safety studies and kids.
- and for places like India, which really, when to eradicate most of their vibeax is relaxing bybacks. It's not from the mosquito, so they are really in gates, is supporting a new point of care quantitative test, so they can test everybody for.
- and start to come in with to fan a quin to really try to eradicate the New Zealand
- in their march towards eradication.
- Right so now we're going to move on to some novel antimalarial therapies. I want to give you sort of an update on malaria vaccines
- and talk a little bit about monoclonal antibodies.
- So we're absolutely making progress in malaria. I do have to give a lot of credit to Bill and Melinda Gates when they started using the word eradication. I don't know. 1015 years ago
- I was definitely in the world of malaria, and I would hear
- the leaders in malaria thinking that's ridiculous. That's never going to happen, Hasn't. He read the literature because there were many, many campaigns to eradicate malaria over the years that failed.
- But I have to say there's been amazing progress.
- and these are all the countries now that are certified to be malaria-free to find is no local transmission for 3 years, but they must have a surveillance system in place.

- So Argentina, recently El Salvador, Algeria, you're still about 35 countries, for where malaria is still endemic.
- In fact, there were still hundreds of millions of cases in 2,020.
- They've recalculated how to calculate that so about 627
- now is in deaths, usually in African children who don't have immunity.
- And now the idea is, hey, Why, don't we go after those really high transmission areas, which, of course, are all in Africa, because the ecological conditions support high transmission water mosquitoes.
- And so this is sort of the new idea for World health organization, high burden to high impact approach. Let's put our resources here, and this is their new goal, reducing malaria, case, incident and death by 90% in 2,030.
- This is really going to be helped if we have a proper vaccine or immunotherapy.
- The other place where a vaccine would be good is places where drug resistance is emerging. So we've done this for a while that there's Artemis and a resistance in southeast Asia.
- This was partly because these were ex-french colonies and trading partners with France.
- which we're using artemisinin as single therapy, despite to who, saying, hey, can we not use artific? And as a single therapy we know there's going to be selection for drug resistance. And so really the original hotspots of Artemis and Resistance are in Southeast Asia.
- and there's really like No, no knowledge on what we should do if there's Artemis and resistance.
- Luckily it's low level. It's a very old paper, but extending the treatment from 3 days of act to 6 seems to do the trick.
- And I think you know, if you look at more recent data, the numbers of resistance is going down partly is, you're trying to just eradicate the parasites by adding a very, very low dose of premium
- to eradicate and block transmission. So when you're using 0 point 2, 5. You don't need to look at G. 6 Pd.
- So I think actually, things are going quite well in Southeast Asia. They're doing quite well with controlling malaria transmission, reducing the numbers.
- So we knew this for a long time. What we worry about is this spreading to Africa.
- And there are some papers with Artemis and resistance, emerging in Amazonia and Eli in 2,020. And then there was this paper in the New England Journal in 2,021 in northern Uganda.
- and they looked at patients treated with Ivr testsinate
- and the way that you
- can the surrogate for our in our test and a drug resistance is, it takes longer to clear the parasite. So when you're doing the smear day, 2 day, 3, you're actually saying parasites for a longer period that should make you concern for drug resistance.
- They did find mutations
- in the region where artificial and drug resistance is associated.
- and what's really interesting is, the mutations are different than found in Southeast Asia, and the reason that's interesting is it means that drug resistance can arise by multiple different mechanisms
- that it's not
- that difficult to arise many different ways. You can get Artemis and resistance.
- This is a problem if it spreads in Africa. Honestly, we Don't have the next generation of drugs.
- People who developed or to miss it in Nevada said, we're going to have second and third and fourth generation, but none of that is panned out.
- So this will be a real problem. This emerges because we don't have the next drug lined up.
- That's why it's even more pressure to develop a vaccine. And this is the excuse slide of why we don't have an anti malarial vaccine.
- and most of it is this profound antigen diversity and parasites.

- They love us, they want to stay in us. They want to avoid our immune responses, and so they keep changing their surfaces. For Zo right has diversity, and then the bloodstream stages encoded by the bargains.
- and that's just a typical of of parasites.
- They they want to avoid Our immune system.
- Another excuse is that every stage has different targets. So the stages in the Sporzoite are different than the parasite protein targets in the blood stage
- or in the meat. You need a side stage.
- And finally, we really don't know
- how clinical immunity develops. If you were born and raised an endemic area.
- you no longer have symptoms. You don't.
- you're not at risk for death.
- but you still have parasites. So if you go to any village in a hypandemic area, 50% of the adults
- have malaria.
- but they have no symptoms. So we don't even really achieve sterilizing immunity in nature, which makes it a higher bar. It's like HIV. People. Don't become naturally immune to HIV.
- That's why developing a vaccine is going to be very difficult.
- So the these are some of the challenges or excuses of why we don't have a vaccine yet.
- But indeed, there's been a large investment in anti-malarial vaccine trials. I just looked this up last night about 206 trials that have been registered by our government, most of them in Africa. Most of them are against Palestinian, which is, I think, appropriate.
- and we all know about our T. Ss.
- This is a fabled and story history.
- The this is the spores all white stage. This is the circumscribed protein, it's the most prevalent
- protein on the surface of the sport is all right, which goes from mosquito into the Dermis.
- and finds its way to the liver. And so, Ruth, this is Wing. I identify this in 1,967,
- and they targeted a part of the Csp. And it's called Rt. Ss
- are for these repeat regions t for what they thought was targeting t cell epitotes
- an s for hepatitis b surface antigen, and the reason they
- throw in the Hepi surface antigen is. It provides a matrix core
- that these antigens can be mixed in to give us a viable vaccine. So it's really just to provide a matrix core.
- The other major
- part of this vaccine is the adjudent, and that's true for probably any vaccine. It's proprietary. It's called Aos one, and honestly for most vaccines. It's going to be the adjuvant that's going to be the winner of the loser.
- So we see a Zillion studies done in Rtss, all published in a journal. We did a phase, 3 trial heroic, 15,000 patients over 6 years.
- And here is the results. So this is Gordosis.
- and the protection was 46% against clinical malaria. There's the confidence interval
- for 7 year malaria, 32%.
- And Wh: how to make a decision.
- Okay, is this good enough data to say we should be using our Tss.
- Does anybody know what they said?
- What would you say? Would you say, yeah, this is this is something.
- Would you say? No, no, no, no, this is just not good enough

00:55:42

risk-benefit analysis

Johanna Daily

00:55:45

is what are the risks associated with. I don't know.

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00:55:52

Okay.

Johanna Daily

00:55:55

how many people there want to go with this? I can. I can count the

- Can you raise your hand if you want to support this vaccine.
- Okay.
- Okay, you guys are just like to. Oh, you're not giving me an answer. And instead, you're far enough to say, hey, how about more data, guys? That's exactly what who said so you guys could all be.
- I'm a blurred.
- They said, oh, we can't decide just like the University of Virginia can't as high.
- and they said to a phase 4, I want you to add it to the standard vaccines that are done in these clinics, and let's see if it works in real life settings. So they asked. The study was in Ghana Kenya and Malawi
- non-study sex study. We're just going to add it to your childhood vaccines.
- and I mean, this is row. 120,000 patients to be followed over 2 years
- feasibility.
- Continue to look at safety and efficacy.
- So you say, okay, now what happens? So
- they looked at safety because there was some meningitis as an adverse event in the original study. There seemed to be excess. Cm.
- and there seem to be excess, mortality and girls versus boys in this larger study. This is not the case, so, as you, said, Sam, safety is numerous.
- They looked at the impact on severe malaria and all caused mortality. It definitely had a protective impact, probably at the same level, about 30 to 40%.
- And in fact, it was okay. They were able to add it to the standard vaccine clinic. It's not like less people showed up.
- So
- Sage Yellow Book, October 2 0, 2, one. So W. H. O. Comes out and says, Yes.
- let's use this vaccine in children in regions in moderate to high transmission.
- and we're going to do for dose schedule.

- Oh, by the way, consider a fifth dose.
- So I don't know if we remember this. We have a lot of press. A few months ago the world's first malaria vaccine. Everybody was excited.
- I mean people here are not. We're all. Not that excited. We want more efficacy, and I I couldn't agree more. On the other hand, we're having an impact with even a 30%.
- So this is like the big breakthrough. Is this other vaccine called the R, 21 matrix.
- And it actually
- has shown the benchmark of 75% advocacy. So what is this faxing? Well, to be honest, it's the exact same vaccine. All they did was increase the number of csp particles.
- and they used a different adjuvant, something called matrix them, which is a sapiden-based adjunct.
- So really based exactly on the same vaccine with a few tweaks. But look at this 77% efficacy.
- I'm sure everybody at Uba would be like. Yes, we're going with this.
- The critique is. It was done at Burkina Faso. Not a lot of transmission. Let's compare it to Kenya, where there's high transmission. Let's give it a real stress test.
- And so this is the latest on our 21 matrix.
- They just published. When you add a fourth booster dose, does it extend efficacy into year 2, and it does.
- There's your confidence interval
- 409, a reasonable sample size still in Burkina Faso, which the critics would say, let's get it into a high transmission area.
- So right now they have an ongoing phase. 3 license your trial 4,800 kids in, you know. Hype, you know a little hyper endemic area, Kenya, which is where the other trials were done. Molly Tanzania
- randomized, controlled trial targeting children, which are at the most risk.
- And here are 3 vaccinations 4 weeks apart in a booster.
- So
- I have to say, I think people that have developed this think it's going to be a winner
- at Trump made this year. They have a documentary film crew. They're ready to be like. We are saving the world for malaria, and I hope they do. But let's keep our eyes open. I think this is really exciting, but I want to see the data from a hyper endemic area to match the Rtss data.
- So Sam asked me to talk a little bit about a monoclonal. So the last few minutes. I want to talk about monoclonal's against malaria.
- and I've learned a lot about one of the
- I had no idea. But these are the best selling drugs in the pharmaceutical market.
- 8 of the top 10 of the best selling drugs for Monica cornels in 18 you can see the predicted revenue, and a lot of these monoconals used for cancer and autoimmune disease. Some of you are familiar with a lot of these we can see in 75.
- And so this area of pharmaceuticals is absolutely exploding.
- and a lot of it has to do with the technological breakthroughs, starting with the mass hybridoma. If there's a lot of new technologies where you can express the antigen of choice, purify it and make it at a high quality grade. And why are monocols awesome. They're very specific.
- very few side effects.
- and you can reliably obtain protective or therapeutic levels.
- And if we turn to Id we've become more familiar with the Covid epidemic. But there are a number of FDA approved monoclonals for Cdf. Rsv. Sars I mean some of they'll come and go depending on their efficacy rabies, and you can see these are now under development.
- So even in infectious diseases, we're starting to get a large monoclonal or humanitarian.
- So monic colonel's are also going to target this for Zoe stage, and people call this the bottleneck that you can see the female an off of these she's not releasing a lot of spores or wife. As a matter of fact, if

- there's good studies, that if she has too many, it's not effective, so maybe 8 to 10
- versus the millions of parasites here. So if you're an antibody or vaccine maker, let's target where there are very few pathogens, so there's no escape. So both the vaccine and the monoclonal are going to target the same target or the same stage or zoites.
- And this paper was published in August 2,002. This was
- tidal fabulous. Does it really tell you what's going on? Low dose subcutaneous, or ivy monocol antibody to prevent malaria?
- They don't say in the title of prevents malaria, because you know, it's only a phase one. But I I like the title.
- So it's phase one so very few patients using a controlled infection.
- They're looking for safety numer uno in a phase one They want to find a protective dose.
- And so what they did was they started with this precursor monoclonal. They immunized a nice volunteer with the whole scores. All right.
- They pulled out individual B cells, and you can take a B cell and find out if it's reactive to your antigen of interest, and that's called reverse vaccinology. It's been done for Ebola and a number of other things. So you can take
- a person has been exposed.
- find their B cell. It reacts to whatever you want in this case is for Zoe.
- And now you can express that make bucket loads of monoclonals, and see if it neutralizes whatever it is. And in this case it neutralizes the sport is always
- so. This was the original publication, of C. One s 43. It looked good.
- And this monoclonal, again, is targeting for zoe it's targeting. This step has to occur for infection of the liver. It has to be cleaved.
- and then it can infect the over. So here's the for zoe Csp. There's a cleavage now. We can infect the hepatocytes.
- and what they did was target that to prevent cleavage they also modified the Fc. To make this monopoly more potent, so I didn't have to give you. Iv. And a lot of fluid. I could give you a very small amount and give it subcontaneous. And the other thing is, they modified it to the half life
- is extended.
- So this is a total breakthrough, because the truth is, we can't give Iv. Vaccines, but we can give subcutaneous. So the study had 17 subjects.
- We received L. 9. Ls. This is the second generation
- versus 6 who did not receive the L. One Ls. But received a placebo. They again looked at safety effectivity. They looked at the half-life.
- and they actually identified a protective serum level. So 88% who received either Iv. Or subcutaneous
- we're protected against infection.
- And really what we care about are the ones who got the subcontaneous, and 4 out of 5 are protected.
- And again they did dose, finding they figured out which dose was needed, and they were able to find a protective level.
- So what's the conclusion on this study? L. 9 ls. They predict a single one. Ml. Subcutaneous injection could provide protection, and infants and children under 5 up to 6 to 12 months, and right now they're into 2 phase, 2 trials in Mali and in Kenya again, targeting children
- out afterwards. And I wonder if they put it in at the same time.
- It's also on a clonal. It also targets for Zoe.
- but it's intravenous, and
- I don't think anyone's going to go forward on it, except to say that this also showed high efficacy. At 6 months 88% were protected after one single dose.
- So vaccine or monoclonal

- Okay, vaccine. We need 3 or 4 we probably need a booster monoclonal, single dose, and you're going to get a robust high level.
- Memory vaccines. You absolutely engage memory. T's and B cells. We don't with the monoclonal.
- which one depends on the host of your response, the vaccine. So maybe if i'm immuno compromise, i'm a little nourished. I have worms. I won't have a good response to the vaccine.
- That doesn't matter for Mcconnell. You're going to deliver a guaranteed therapeutic level.
- Resistance is an issue for both.
- So my last slide here, so I I feel like both the r 21 is exciting and a breakthrough. I think the monoclonal is a breakthrough, but we have to figure out where to put those.
- maybe during outbreaks where we can't put, you know, 4 doses.
- maybe chemoprophylaxis in special populations. Maybe people who are deployed to the field.
- maybe under 5 for that season.
- or maybe pregnant women.
- So this, you know, let's see where this is going to be deployed.
- But let's also look for the phase 2 trial.
- So I think i'm going to stop there and see if we have any questions in a remaining few minutes

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01:06:51

i'm with.

- I will, I'll kick us off with a question. Our Id Journal Club for the residents read the Monoclonal antibody study in Mali.
- and one thing that kind of struck me was
- you had mentioned before in hyper endemic regions. People Almost 50% of them are infected, and they're asymptomatic.
- and that requires them to be exposed and build an immune response to it.
- And so for patients who are getting an immunoglobulin, and then are deprived of the chance to receive, to develop a true immune response
- to an endemic disease.
- Is there any sort of ethical issue here at the fact that
- by the when the studies are done, and no more immunoglobulins available. These people are going to be at a very high risk of getting severe disease.
- because they're going to be. Essentially patients should
- lived without being exposed to it.
- Does that is that play a. Does that play a role? Or am I just kind of thinking about the immunology wrong here?

Johanna Daily

01:07:54

No, I think that's a that is a wonderful question. But the studies already been done, and it was done with

- layer, chemoprophylaxis. So right now, if you live in a hyper endemic area. All children under 5 are given malaria chemo prophylaxis, and I think people were worried about that as well.
- Right. So once I hit 5, and i'm not giving them their anti malarial. Are they all going to die of cerebral malaria? And the answer is, no, probably for 2 reasons, one none of these therapies is 100% protective against infection. So maybe you're getting a little bit of immunity.
- And secondly, I do wonder if
- neonates and children, you know there's find this Isn't fully developed until age 4. Perhaps if I now made it to age 7,
- my immune response is a little more competent. But I think
- your point is well taken. In fact, maybe the monoclonal is more robust, and they will never get even a small infection to gain immunity.
- We'll They'll follow that closely in trials.

Unknown Speaker

01:08:55

sure. Okay.

Unknown Speaker

01:08:57

Thank you.

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01:08:58

We have a microphone in the center here. If anyone has a question they want to ask from the audience as well.

- Yeah.
- one of our chief residents is coming up Chelsea now.
- Thank you so much, Dr. Daly. So you were to discussing the Monaco and the antibody and the vaccine, which are both very exciting.
- I wondered if you had dots about the potential sort of cost impacts of these we know that monoclonal antibodies can be particularly for expensive to produce, and given the duration of a protection kind of.
- as you mentioned, picking, the population would seem to be particularly important. But what do you see in terms of resource dedication? So where we're putting our dollars as we're developing these these therapies

Johanna Daily

01:09:41

Thanks. I have to say I, a a colleague of mine, who makes Monoconals Cardiac shanron. He made it against Ebola. He pushed me a couple of years ago. Let's do a monoclonal against malaria, and I, of course, said, oh, that's a terrible idea, but I've I've made a lot of mistakes like that my life, and one of them was I.

- What the monoclonal is like $20,000 for one dose for many of the things that we use in the clinic.
- However, I talked to a friend of mine who works in Big Pharma, and I said, You know how much is a monoclonal, and he thought with today's technology and production.
- They could actually be a lot lot cheaper. Because I agree with you when I hear the word monoclonal, i'm thinking $1020,000.
- Apparently they can be produced in large amounts
- for reasonable price. And I think it has to do with all these breakthroughs in the new technologies.

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01:10:34

Okay, that'd be great.

Johanna Daily

01:10:36

totally.

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01:10:44

Have you guys seen any malaria down there? Anybody in the Audience.

- Yeah, yeah. Hi, Joanne Kostie Sephere. Good to see you. Excellent, fantastic talk. I just. I was curious. If you could talk a little bit about artisanate Artemis, and and that was very interesting, I think, is very interesting data concerning resistance in Africa. What do you see is the future there? That's a a concerning development

Johanna Daily

01:11:14

totally. Now the thing is in Africa. They still have quinine, and what I've always been sort of puzzled about is.

- I don't think there's a lot of quinine resistance, and I don't know it's because it's not deployed at a great level, but I think it is.
- Africans often have a lot of side effects with quinine, so maybe it's not being used

- broadly. I feel like quinine is still in our pocket. I don't see a lot of quinine resistance, and again it's still available in Africa.
- so that mall around we could still use that, although apparently malarone resistance develops pretty quickly. So I worry about that. Mallory is very expensive. I don't see it being deployed a lot in Africa. But I think
- that should still work.
- Maybe. Gosh! Monoconals to treat malaria.
- Maybe now that we're talking about it, we we use monoclonal to treat Covid actually, maybe model calls.
- That's that's an interesting idea.
- Right now. The level of our
- Artemis and resistance, at least in Southeast Asia.
- just extending
- the
- duration works.
- The parasite is so unbelievably smart.
- Artemisines have incredibly short half-life, and they only work in the later phase of the parasite development. So the ring stage
- our testinate or to miss it in doesn't work. So what it did was prolong the ring stage until
- or or testinate
- cleared in the bloodstream, because it's a very short half-life. So it was kind of brilliant that way, but once it gets to the later stage the troph and tries on
- it's very effective. So I think the good news is, we probably can just expand or extend the duration of treatment.
- Will the shizont or troph eventually become resistant? Probably, yes; but right now that doesn't seem to be the case.
- maybe Mall or maybe monoclonal's. I think there are a bunch of other drugs coming down the pipeline, but
- I haven't seen them really in phase 3. Yet. I think people are worried about this.
- I I see a fantastic question on the chat about any update on cerebral malaria, which is what I work on.
- A couple of things. It looks like brain spelling for sure is resulting in cessation of breathing in these kids.
- which is great. We finally have a reason why they are dying. But then you say, well, what should I do? Try to get mad at all. Well, there's studies of mad at all using in terms of therapy. Kids did worse, but when they did those studies they didn't new head brains flowing. How about high salt? Should we use that if we have very high volume swelling?
- Those studies are underway? So I don't know what to do about cerebral malaria
- high swelling.
- The Us. Travelers that die of fel superim also get this manifestation this first described in Malawi, I think 2,015. So I don't know what to do about that, except to look for that brain swelling
- definitely. Get articulate asap.
- So that's we still have to figure that out. Our lab also works to try to identify junction therapy. 2,600 trials failed.
- We're studying dimethyl pummerate in the animal model.
- So I think we need a jump to therapy for Cm: and we need to know how to manage brain swelling. I think it's still not known.

01:14:45

Okay, I don't see any more questions here in the chat.

- I think our we we've asked our questions here in the audience really great talk Dr. Daily. I thought this was fantastic, you know. I think you certainly have done this talk before. It sounds like very well practiced and great audience participation. This is great, thank you.

Johanna Daily

01:15:09

Thanks, Sam.