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"The Burden of Neurocysticercosis in Endemic Areas"

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Hélène Carabin: My name is Hélène Carabin. I'm an Infectious Disease Epidemiologist. I work at the University of Oklahoma Health Sciences Center as a professor. My background is in veterinary medicine, so I have a DVM from Montreal. And I did a master's in veterinary epidemiology and then the PhD in human epidemiology.

I think that my background has brought me to being particularly interested in zoonotic diseases, and especially parasitic zoonotic disease.

What I wanted to talk about today is not necessarily our projects in Burkina Faso, India or South Africa, where we've been working at, but more talk a little bit about how one could try and measure the burden of neurocysticercosis, and cysticercosis.

The reason why this is an important question is, as you know, a lot of people are now looking at the new disability adjusted life year estimates from the Global Burden Disease Group to decide which disease should be controlled as a priority. But they have different ways of measuring burden. DALY is just one.

So in order to measure burden, one has to have some information about a disease. That's a little bit about what I will be talking about today specifically.

The first thing, I'll just go through the life cycle of *Taenia solium*, because although some of you may know it, some of you may not. And even the life cycle and natural history is not completely known for that disease.

Then I'll talk very briefly about the evidence that we have in terms of control and eradication of the disease. Because as Joe was saying before, the WHO has cysticercosis as one of the disease that's eradicable. So I'm going to discuss a bit about this.

Then I'll present some results from meta-analyses that I've conducted with my group to try and evaluate the frequency of cysticercosis and neurocysticercosis, as well as how it manifests itself. And is it deadly? What do we know about the duration of this disease?

And then finally, I'll go through different ways one can try and measure the burden of neurocysticercosis going through what has been published so far in the literature. As part of it, I'll also discuss a suggested approach to try and improve these estimates of DALY's in particular, and possibly the monetary burden of cysticercosis.

To start with, what people refer to the as the pork tapeworm is actually a human tapeworm. The human harbors the definitive host of the adult form.

And that's a really neat picture that I found on the internet where you can really see the head of the tapeworm and the different segments. And the segment that's open-- all the little dots here represent the uterus of the worm and each small dot is probably one egg.

So each segment contains several hundred thousand eggs. And they are being shed with human feces. And as you can imagine, they contaminant the environment immensely every time someone defecates in the environment. The eggs, themselves, are shed into the environment, as I said. And infected humans-- so humans with the adult worm-- are believe to shed about five proglottids per day and each one will contain between 30,000 and 90,000 eggs.

What is very, very tricky with these eggs is the diagnosis of taeniasis, so the diagnosis of humans with the adult worm, is very difficult. Because under the microscope, *Taenia* eggs really look alike, especially the eggs between *Taenia solium* and *Taenia saginata* cannot be differentiated under the microscope.

There is a coproantigen test, but even that will not differentiate between the two worms. The only way to know this is PCR, or purgation of people who are positive and then identification of the head of the worms. As you can imagine, in terms of an epidemiology study, this is not really feasible, because it's way too expensive.

The pigs who will have access to human feces may get infected with the eggs. These eggs become metacestodes, or larvae once they enter tissues of the pigs.

As far as we know, pigs are the only intermediate hosts, even though there's been reports that dogs could be intermediate hosts but that has not really been confirmed.

So in pigs, it may be 10% to 20% of pigs that are infected, mostly those that are really heavily infected, you might be able to see a cyst under the tongue in a pig that's alive, but that's really not easy. This is a pig that's really, really infected. You could potentially see the differences.

Now what's interesting, in some cultures people will actually enjoy eating pork meat like this because they will feel-- I think it's in Bénin that I heard that-- they feel that these cysts when you have them in this meat are really good, because they're succulent because they have a little bit of juice in them. Culturally speaking, it may be a little bit challenging to control this disease and change that culture. People are really enjoying the pork when it is like this. Proper cooking of the meat will kill the larvae in the meat. It's when the meat is not properly cooked that humans can get taeniasis so they can get the adult worm.

Now what's interesting about *Taenia solium* that does not happen with *Taenia saginata* is that human can infect other humans. The egg in the environment, if ingested by humans, will do as they do in the intermediate host-- the pig-- it will migrate to different issues. And where they migrate in humans are similar to pigs. In some cases, they may end up in the muscles.

This is an x-ray of someone that has multiple calcified cysts from cysticercosis in their body. They may end up as subcutaneous cysts, like this case here.

Or, what's more concerning, is, in some cases, and no one really knows what proportion of cases, the larvae can end up in the brain. And when it ends up in the brain, it can be associated with all sorts of symptoms which I will go through later on.

So to summarize, this is the life cycle of *Taenia solium*. This is my little cartoon-ish version of it. But what's interesting is if we start with people that have taeniasis and who contaminate the environment, the time that eggs survive in the environment is unknown. It's been reported between two years, some people say it's up to five years, but it highly depends on temperature, humidity, et cetera.

The other issue with this is that there has not really been experimental studies on *Taenia solium* eggs, per se. Most of the studies are being done on *Taenia hydatigena*, or *crassiceps* or *saginata*. But there's been very, very few studies, if any. Well, in vivo, anyway. There have not been any studies on *Taenia solium*. So we don't really know how long that egg can live in the environment.

Once the pig gets infected, it will take from 10 to 12 weeks for the larvae to migrate and mature in the muscles, after which a human may eat that undercooked meat. Now they may or may not develop taeniasis, but if they do, it will take two months for the larvae to become an adult worm in the intestines of the humans. You can see we have at least five months here, just between the pigs getting exposed to human feces to a new human case.

Another point to make is that the eggs are infectious at the minute they are shed in the environment for those that are mature. Now when humans infect other humans, a human with the adult worm can infect themselves if they don't wash their hands properly. But they can also infect other people through the environment or through food, et cetera.

In humans, very similar to pigs, it may take between 10 and 12 weeks for the larvae to migrate to the tissue and then become a cyst. Now the time between exposure and the development of cysts and symptoms in the brain has been reported to being anywhere between less than a year to thirty years.

So might as well say that we know very little about the natural history of the infection because it's nearly impossible to know who gets exposed to the eggs. It's very difficult. And in terms of an epidemiological study, it would really require a very solid cohort study, which to my knowledge has not really been done yet.

By the way, if anyone has questions please ask your questions as I go. Are there any questions so far?

Joe Perpich: Why is there so little known about *T. solium* eggs as opposed to the other forms of the disease?

Hélène Carabin: There is the slide right here that might answer your question. It's actually quite hard to get the eggs. Because first of all, in human populations the prevalence of *T solium* is fairly low. It's probably in the order of between 0.5% and 2%. when it's really, really bad. So first of all, you have to find the humans that are contaminated with the adult worm. Then you have to be able to purge them. Then you have to be able to get the eggs. Then you have to be able to figure out how long they survive.

Now in the environment proper, all *Taenia* eggs look alike. So unless you were to really put the eggs in the environment you could not go in the environment and try and say is this *Taenia solium*? It would be very difficult. It might be feasible, but it would be very difficult.

and most of those studies of survival of eggs in the environment all date from the '60s and '70s.

I tried to find better data. I didn't find anything. There's more on echinoccocosis as I said, *Taenia crassiceps*, a little bit of *Taenia saginata*, but really, I have not found anything on *Taenia solium*, or very little. If any of you do know something, please let me know, because I'm trying to figure this out.

But for example, that group, Gemmell, one of the things they said is that the eggs would get killed at a temperature of 38 degrees. I have my suspicions about that, given the human body's about 37 degrees. I don't see how the eggs could get killed at 38 degrees. This was in vitro, so who knows what happens in the environment.

The other issue, why we know so little about the natural history of the disease is that it appears to be fairly difficult to experimentally dissect pigs for the same reason it's not easy to get the eggs from the infected humans.

I know the Peruvian group has an experimental model for pigs. But I don't think many more people were successful in doing this.

Now the other reason why we know so little about the pathophysiology and the natural history is the only reasonable diagnosis tool is imaging-- brain imaging. It can be CT scan. It can be MRI. But you cannot really do this on people who are symptom-free, especially CT scans, because of the radiation. Now, MRI, in areas where it's endemic, most of the time there's not an MRI and the price of MRI will be prohibitive.

This comes back to a question that Anna Sanchez had sent in advance. One of the reasons why we know so little about NCC is that immunoserology is not very good at predicting NCC. The sensitivity and specificity for NCC is not perfect. The specificity, because some people may have

larvae elsewhere in their bodies, therefore they may be CC positive, but have nothing in their brain.

And in some cases, people may have old lesions in their brain that are calcified, that are still associated with symptoms, but the serology may be negative because they were infected too long ago. Or it has not gone through the blood brain barrier. So it's really a very difficult disease to diagnose, especially in countries where it's endemic, where access to brain imaging is limited.

The last point. I've already mentioned that we don't have much literature on environmental factor influencing of the survival of the egg. That would be very helpful to know.

There's been a reasonable amount of literature on the control and elimination of *Taenia solium*. And as I said previously, *Taenia solium* cysticercosis is an agent considered eradicable by the WHO. As far as I know it's the only zoonotic agent that is considered eradicable.

Now problem with this is, and I will show you the evidence in just a little bit, there has not been, to this date, any community-based randomized controlled trial on effectiveness of control strategies to control human cysticercosis.

Again the Peruvians have done something. But the results have not been published yet. And I was not able to find them.

On porcine cysticercosis there's only been two community-based randomized control trials. And I will talk about them in a minute.

The reason why the WHO considered it eradicable is, I think, they just used the same approach as for soil transmitted helminths possibly? It's just natural thinking, the prevalence in humans is pretty low, therefore we can just treat all human with mass drug administration and we'll get rid of the disease. However, the evidence is not there to support this.

The other thing is the prevalence is so low that if you miss a few people they will continue to contaminate the environment. Plus we don't know how long the environment remains contaminated for. So I'm not entirely sure how they came to that conclusion. And I think they may be revising that recommendation. Although it would be good if they could do it, but I'm not sure if they will.

In terms of evidence of effectiveness of strategies to control human cysticercosis and taeniasis, I found five reasonable studies-- I did not include them all because some were just not worth bringing to the table. But none of them had a control. All of them were comparing prior to some sort of an intervention to after that intervention at a community level.

Probably the largest study is the one from Medina in Honduras that was recently published-- I think it was 2011 or 2012. What they did is, they looked at pre-post prevalence of neurocysticercosis among people with active epilepsy. And they did that in a large area called Salamá in Honduras. And the intervention included education, safe water, toilets, child clinics, mass drug administration of Albendazole to children and taeniasis surveillance.

The authors report that the cost of this intervention would be in the order of 1.3 million. Most of the intervention took place, like the MDA implementation and *Taenia* surveillance, toilets, et cetera, took place in 2001. And what they found is that the proportion of NCC among people with active epilepsy went down between 36.7% pre-1997 to about 14%, post-1997. So it appears that what they did really worked.

Now most of the other studies looked at taeniasis. I think these three. The problem with a lot of those is they used coproscopy to diagnosis taeniasis. And coproscopy is has very little accuracy. So even if you reduce infection a little bit, you may not capture everybody who's infected.

And the other study in Mexico, they did find some reduction of seroprevalence, but very little, by treating *Taenia* carriers with niclosamide and praziquantel. So there's really nearly no evidence. At least from a randomized trial there's no evidence of what might work to control human cysticercosis, taeniasis or NCC.

Again, the closest that we are is from Medina. But the study was pretty long. It was over eight years. Can we attribute all of the reduction to these interventions?

But if they had, had a control group in an area in Honduras where the socioeconomic status has gone up, would NCC decreased as well? This is something that we can't tell from those studies.

Now in terms of evidence there has been some community-based randomized control trials control porcine cysticercosis. And the two at the community level were done in Peru and Tanzania.

Now in Peru, they treated the humans with praziquantel and the pigs with oxfendazole. And they found that cysticercosis in pigs was reduced. However, there were a lot of problems with the designs of that study. A lot of the randomization got broken. There was contamination of the intervention. And the statistical analyses that were used were not proper. So it's difficult to say really if it worked or not.

Now, in Tanzania, there was a randomized trial in 42 villages where the treatment was purely educational - education of farmers to see if it would reduce porcine cysticercosis. And after two to five months of follow-up of sentinel pigs, the infection was reduced with an incidence rate ratio of 0.57, so by almost, not quite 100% but almost.

So these are the two community-based, and it looks like education, itself, without any drugs, might be able to reduce porcine cysticercosis somewhat.

Now, there's been other trials, tests, oxfendazole, and a vaccine developed by Lighttowers group, TSOL18 and TSOL16. The vaccine seems to be working very well, especially when we have at least one or two boosters, whereas the oxfendazole works as well, but almost the same level as the education was working, which I found was quite interesting.

Now, of course, what's interesting as well is that if you want to treat pigs with oxfendazole or vaccine it's going to cost a lot of money, because pigs are born every day. So it may not be as sustainable as the educational treatment.

Someone just mentioned that the Garcia trial is still ongoing. It was supposed to end in May, 2013. So I'm really hoping that we'll see some results soon.

Just to summarize what we know about control, at this time we don't have a lot of evidence as to what works to control human cysticercosis and neurocysticercosis. And Ana Sanchez has confirmed that Medina did not control for confounders in the study. But it seems to be working somewhat. But we just cannot get a number on it.

Now porcine cysticercosis can be reduced by 2 doses of vaccine or through education and oxfendazole. But we don't know how that impacts human infection, which is what, ultimately, we would be interested in.

But what do decision-makers, public health workers, politicians, what they want to know is what is the relative burden of cysticercosis compared to other diseases? Is it worth their buck? Should they invest in controlling this disease instead of malaria, or instead TB, or instead of HIV? Why should they put money in controlling it?

This is where the measurement of burden can be helpful. Now burden can be defined in all sorts of different ways. Some people use mortality itself. Some people use morbidity. But the most commonly comparable measures are those of health adjusted life years, sometimes referred as utility when we do a little bit of math with them. And these include quality adjusted life years-- QALYs, disability adjusted life years-- DALYs. And one can also look at the monetary impact to do cost benefit.

When we use the QALYs, it's really something that's based on the individual perception of their own health.

DALYs, in contrast, is really meant to be a global measure where everybody is the same. That is, a blind person in Tanzania would have the same disability as a blind person in the US. So it's really meant to compare if everybody in the world was exactly the same.

The advantage of the monetary impact, since cysticercosis is a zoonotic disease, this allows us to look at the impact of the disease not only on humans but on pigs as well. So it really gives a global view of the social impact, monetary impact, but the whole society of a disease that, such as cysticercosis, impacts agricultural sector and the human health sector.

Now all of those measures require the following information: the prevalence or incidence of the infection or disease, the distribution of the sequelae-- that's the Global Burdens of Disease jargon-- or symptoms associated with the infection (cysticercosis), death rate, and duration of symptoms.

Now when our group was asked by the WHO to review the burden of cysticercosis, the first thing that we had to do was to try and figure out how frequent is it. What is the prevalence, let alone the incidence? But at this time, there was absolutely no cohort studies, so the best we could do was prevalence; and try to figure out what distribution of sequelae. And that had never been done in a systematic way.

So this is what we started doing. We conducted two systematic reviews. One to look at the frequency of neurocysticercosis and the other one to look at the distribution of manifestations among people with NCC.

We looked at Pubmed using MeSH terms, and we also looked at CAB and another 23 international data bases because we didn't want to miss anything. And we really tried to include as many languages we could cope with, so English, Germany, French, Spanish, Italian, Romanian, Portuguese, and Chinese. At the time, we did that a few years ago, so we limited between January 1, 1990 to June 1, 2008.

The first systematic review was to look at the frequency of NCC. I'm not going to go through all the details here, but we identified 565 papers. And we reviewed the titles and abstracts of all of those. We identified 290 possibly eligible articles for the inclusion in the systematic review. And of those, only 23 were included.

Most of the excluded criteria were due to poor design, selection bias, and no imaging. No imaging was a big problem. And it's really a shame, because it's in countries where it's most endemic that there's the least access to imaging. Unfortunately to really diagnose NCC, the serology's is not very good, and one really needs imaging.

This gives you an idea of the distribution the articles that we found. This is all the ones we reviewed the abstract and titles for. And you can see already in Africa there should be a lot more, especially the non-predominantly Muslim areas, there should be more articles there. There, it has not been published. And see here is what ended up included. So most of the studies were in Latin America, some in India, and a few in Africa.

So the first thing we did was to try and figure out what is the proportion of NCC among people with epilepsy. And I added here in areas endemic for it, because, of course, people when they study NCC, they're going to go where they know that it's present. So if I put a country name, it does not necessarily reflect the proportion of NCC among all people with epilepsy in that country. It reflects the place where it was conducted, and that's important to know.

However I was stunned when we saw the results see to what extend this is consistent. I was expecting to see anywhere between zero and 100%. But amazingly, everything was really hovering around that 30% mark.

I think we're fairly confident that across the world where NCC is considered endemic, about 30% of people with epilepsy will have lesions of NCC in their brain. Is NCC the cause?

We can't tell. It's always cross sectional. But it's likely to have something to do with it.

What this next slide shows is the distribution and proportion of NCC among people with epilepsy by age. Because in the past, some people have reported that NCC was not as important in children. But when we stratify it by age, but the only cut-point we could use was 19 years old, because of course, each study will have their own cut points, but if we look at children and young adults, say of 19 and less, the proportion was at 25%. But a confidence interval between 18 and 32, whereas an adult was at 28% with a confidence interval between 20% and 30%. Nearly the same.

So I don't think we can say that NCC does not occur in children. It's probably just as frequent. It may not start in very, very young children, like at two years old, but certainly after four or five, it's present.

So in conclusion from that first meta-analysis is, we were able to only include a few studies, unfortunately, because of poor access to imaging in developing countries, and also poor study design.

Some studies were only looking at volunteers. We did not include those because we felt the selection bias was too high. And most of those studies were conducted in Africa or poor areas in China. China was one, there was a lot of studies but nothing was good enough to be included.

However what was included, I think that we can say is that about 30% of people with epilepsy have lesions of NCC.

The most recent papers that I've seen since then, they all still come back with that similar estimate. Our problem right now is if we want to measure a global burden of the disease we need to know where these endemic areas are. And I don't think anyone knows.

The second systematic review was to look at the distribution of sequelae among people with NCC. So in that case, we identify 1,568 papers for which we reviewed titles and abstracts. We reviewed 404 articles, in full, and included 21.

What this meta-analysis showed was -- first of all, one has to know that this was mostly based on case series of people with NCC. So it's not really representative of all people with NCC. It's representative of people with NCC who ended up in a facility where there was imaging. So this is a caveat of that review.

Among those who end up in a neurological clinic or a clinic where there's radiology, or imaging, about 80%, their main complaint at presentation, or one of the complaints at presentation, was seizures or epilepsy.

What's interesting is this was more common in children than adults. And the difference between the 79% and 63% was significant in a meta regression. So adults will less often present with seizures than children.

Another thing that was of interest is that, overall, almost 38% of people with NCC present with severe, chronic headaches. And in prior measures of burden this has not been considered all that often.

Another part that's not been studied as well is, people who present with depression, because it's a mental health issue, so it may not be captured. Or it may not be reported in the papers. But that's something that one would have to review carefully.

And why is that? It's because in their most recent Global Burden of Disease estimates, depressive disorders, I think, are ranked third in terms of burden. So if NCC is responsible for some of this it should be allocated to NCC and not depression, itself. This is something that's very difficult and that we would need to have an ongoing discussion with the Global Burden of Disease Group to see how this is done.

Now the other question that one may ask is, are symptom always present among people that have NCC lesions in the brain? And the answer to that is I don't think anyone really knows. There have been studies, however, conducted on that topic. In particular, the only study that really used simple random sample of people in a community, that just randomly sampling people, sending them for imaging, was conducted in Mexico between 1999 and 2000. And they found that 9.1% of the people that they scanned had NCC lesions.

All of them were calcified and these people could not recall symptoms. It doesn't mean they never had symptoms. Maybe they had one seizure. If someone had an absence seizure or a partial seizure it's not obvious it would have been diagnosed. But this is what they found.

Now other studies have had not used simple random samples. But still, there are reports of NCC among people EITB-positive. Now in that case some people had some symptoms. But all of this said, no one really knows if everybody with NCC will eventually develop symptoms or not. So this remains a question mark.

The next question was, since death rate is important for all these measures of burden we tried to review in these papers if NCC has been reported to kill. There's very little data available on this topic. And they're very difficult to interpret because the studies we reviewed were from case series.

So all the people are under care. Therefore, if death rates are reported, they're among people under care. So we don't really know what the death rate among people who are not under care might be. It's likely to be higher in these populations.

The deaths that are reported usually occur, at least among people under care, among people with ventricular or subarachnoid cysts or people with hydrocephalus that had a shunt.

The proportion of death among these patients varied anywhere between 0.9% in Houston that was everybody to 18.5% among children in India. They've all had partial seizures in that study. I would say that most of those studies reported about a death rate of around proportionate death of about 3%.

Now we also found three studies that reported death rate in the whole population related to NCC. But this is based on the official death certificate, so it's probably an underestimate. And that's been reported to be anywhere between 0.33 per million in the US to 1.7 per million in Brazil. Again, these are probably quite largely underestimated. But, it's a minimum. We can say it's at least that.

Now the duration of symptoms with NCC, this is really difficult to assess. So the best we can get is from those case reports or case series where they've asked people for how long have you had these symptoms whenever they seek care.

Honestly, it's all over the place. In South Africa, the median was reported at 56.8 weeks, so just over a year, but a maximum of more than ten years was reported. Even in the US, the range was reported to be between zero months to 41 years.

Now was the initial cause of epilepsy 41 years prior NCC or something else? It's nearly impossible to say. So I'll just say the duration of NCC remains largely unknown in the absence of natural history studies, which would not be ethical to conduct anyway. But this means that for burden estimates it's very difficult to do.

So to summarize here, I think that we can say that an average of 23% and 35% of people with epilepsy have NCC lesions in endemic areas.

Epilepsy is not the only symptom associated with NCC. This is something that we should really start looking into a little bit more carefully. Especially stroke has been reported in one study among, I think it was about 17% of people with stroke were reported to have NCC. And NCC lesions were really identified as causing the stroke. If this is the case, the Global Burden of Disease aspect eventually could be much larger.

Severe chronic headaches are quite common and the depressive disorders could potentially be very common.

People with NCC can die, but we don't really know what that rate is. The duration is not very well known. And we still don't know where the endemic areas are. So whenever we'll come to the burden assessment with DALYs and monetary burden we have to rely on a huge amount of assumptions.

How can we get to the burden from there? When I tried to find literature on QALYs associated with NCC, I was only able to find three studies. If anyone knows of anything else I would be very interested in knowing that.

The largest study was conducted in Mexico where 220 NCC outpatients seen in two tertiary hospitals-- so they were really severe cases-- were compared to 220 gender-age- hospital matched individuals that were accompanying people without NCC. In this study, people with NCC were worse off on all domains of the quality of life then the controls.

The other two studies compared NCC patients with either people with the same symptoms, or with epilepsy or headaches, but that did not have NCC. And in that case, they didn't find a difference. However, the sample sizes were not huge, but still considerable.

The third study only included 14 NCC cases, so it's very difficult to interpret. But they did find that people with NCC were a little bit worse off on social functioning than controls. What this figure shows is result that we got from Mexico. And it shows the scores on the different domains of the QALYs of the controls compared to the cases. And you can see that the NCC cases, basically, had lower scores on all of the domains, physical function, role physical, bodily pain, et cetera.

Now when we stratified the results by different characteristics, what was interesting to me is that people with epilepsy and NCC were not statistically different from the controls on the physical component of the QALYs. But they were on the mental component. Whereas those with hydrocephalus and severe headaches were different.

The other thing is that when we stratified by the time since diagnosis people seemed to adapt physically to NCC. So that people who were diagnosed six or more years ago were not different for the physical component, whereas those that were diagnosed less than six years ago, they were different. But they all differed on the mental component, meaning that NCC really has a very important mental component to it that has not been explored enough, in my opinion.

So to summarize the studies from QALYs, it appears that NCC patients have lower quality of life than people without neurological disorders. The study from Mexico used very severe cases of NCC, although they're under treatment. But it's probably the largest difference one could find. However, once symptoms are present it seems that NCC does not add any worst quality of life aspects that people with the same symptoms that do not have NCC.

Now the next types of studies that I have included were those that looked at DALYs associated with NCC. And for this, there's only been three studies. One in Cameroon, one in Mexico and the last one is latest Global Burden of Disease assessment that was published in December in the Lancet.

Now all of those studies, as I said before, they have, like, one page of assumptions. I'm not going to go through them. All I can say is the assumptions made by the Global Burden of Disease Assessment are very hard to figure out. I'm still trying to understand what they did, because I worked with them on it. We still need to communicate a lot more to try and improve that estimate.

But what we can say is that in Cameroon, the DALYs per 100,000 person years estimated -- no, sorry, this is the total DALY, it's not per 100,000, was estimated at 46,000. In Mexico, it was estimated at 25,000. In the Global Burden of Disease total in the whole world was estimated 503,000. This tells me that the Global Burden of Disease was probably underestimated, because just the sum of Cameroon and Mexico is 70,000. So it is very unlikely that the whole world would be at 503,000.

What I can say from this is the Global Burden of Disease estimate is an underestimation. We have to work with them to make this better. But the problem that we have to get a proper estimate is that we don't know where the endemic areas are. We also don't know how common the other symptoms are. We have an idea. But the DALYs estimate of-- well, first, there are only three studies-- two of which only included epilepsy. The third one included epilepsy and headaches.

But if these are to be included-- the other symptoms-- then again, we'll have to talk with the Global Burden of Disease Groups, take away neurological symptoms attributable to the neurological group and put them under the burden of NCC. And that could be difficult. So we suggested an approach to try and improve the Global Burden of Disease estimates. And if anyone has feedback on that I will be interested in knowing this.

The first thing that we're trying to do, and this is what the student of Christine Budke, at Texas A&M, would be to try to use surveillance, hospitals, sero-survey data to model where cysticercosis is, at least maybe, maybe NCC, and then use environmental factors, ecological factors such as sanitation, unimproved sanitation, pig population, distribution of religion to, estimate the population at risk and then regress those factors on seroprevalence, where ever this is available.

The problem is this is not available in a lot of countries. Although this is something we will try to do with seroprevalence for Burkina Faso and I currently have students working on that, including Amina, how we will try to do.

Now don't be scared. This is a possible way that we could try and get a more inclusive, or comprehensive, burden of disease estimate. And the idea is to start with epilepsy. From epilepsy, we can get NCC epilepsy cases given our meta-analysis from endemic areas. And I know that the number of epilepsy cases is supposed to be available from WHO. We're trying to get that information.

Once we have cases with NCC and epilepsy, we can back calculate the total number of cases with NCC that are seen in neuroclinics. Based on the second meta-analysis we can end up with NCC cases with all sorts of different outcome. I'm not going to go through all of this because it's complicated.

But I will give you an example of what Rachana Bhattarai, in our group, did in Mexico. We stratified the population of Mexico in urban and rural population as well as we did gender, I believe. No, it was age. Sorry, it was children and adults. And then we multiplied by the prevalence of epilepsy urban, rural areas, children and adults, to calculate the number of epilepsy cases in these strata. And then after that we obtained the number of epilepsy cases.

Then we looked at the literature to look at what proportion of epilepsy cases are seen by doctors in rural and urban areas in Mexico to estimate the number of cases under care and not under care. And with this, we were able to calculate the number of DALYs for NCC associated epilepsy. Because there are disability weights for epilepsy cases that are under care and not under the Global Burden of Disease.

Now once we have that number of NCC epilepsy cases in this different strata, if we divide that by the proportion of NCC cases with epilepsy that are seen in rural clinics, about 80% overall-- 80% of children-- maybe 63% in adults, we can get the total number of NCC cases seen in neuroclinics.

From there, we can get the total number of NCC with severe chronic headaches. If we divide by the proportion of those cases that seek care, we get the total number of NCC cases with severe chronic headache. And then we do a similar approach to what we did for epilepsy and we can get a DALYs estimate for NCC headaches.

Now we use disability weights for migraines, which may not be exactly the same as severe chronic headaches reported with NCC. But that's the closest we can get to an estimate.

So this is the approach we would like to be able to use in other areas or countries. So if any of you are interested in doing something like that, that would be great. And we could try and improve the estimate of DALYs of NCC.

I just wanted to show this graph. This is called the tornado graph, is when we conduct these types of study we have to include uncertainty.

And how certain are we about our DALYs estimate in Mexico? The answer is not so much. Because there's so much uncertainty. The most uncertain point in our analysis was the disability weight for epilepsy, because we didn't use an exact value. The prevalence of epilepsy was another factor.

Until we have better epidemiological data, any DALYs estimate will remain very uncertain.

I'm going to go through this one fairly quickly because we're starting to run out of time. But I just wanted to talk briefly about studies that looked at the monetary burden of NCC.

I could find two studies that look at the cost of NCC cases. They're not population based, so they just looked at patients with NCC. And they look how much it cost.

There was one study in Peru in 2002 and one in India in 1997. I think that's when the year of costing was done. 49 cases in Peru. 59 in India. And the estimated total cost of $996 per case in Peru and $170 until resolution in India. Of course, there's about five years' difference between the two. And there were less costs included in the India study. Then this is probably why it's a little bit less.

Now in terms of population based studies, and these are the nice ones because they allow us to include the cost to the agricultural sector, so loosing value of pig carcasses, if they're inspected, or having a reduction of the prices that one can sell their pigs for if they're infected, etc.

There have been four studies like this. One in Cameroon. One in the Eastern Cape province of South Africa. One in the US, which was interesting to me. And another one, very recent in Laos, but that's very hard to follow. I'm still trying to figure out exactly what they did.

Just to give you a ballpark, the figure was used for the estimate in Cameroon and the Eastern Cape, and in Cameroon, they ended with a cost of nearly $13 million per year. And in the Eastern Cape, about $18.5 million. So very similar estimates. The estimate per person was very similar between these two countries as well, which was quite interesting to see.

Most of the costs remained on the human side, although there were some animal costs. The reason being that very few farmers send their pigs to the slaughterhouse. So most of the time if the pig's infected no one ever knows. So the loss is not that important.

Now the study from Los Angeles County, the US, is really interesting because it shows that even in developed countries such as the US, NCC can have an important impact. And here they estimated an average of 7.9 million per year for NCC cases in Los Angeles County. And it's important to know, as well, that a lot of those cases may not have medical insurance because they would be immigrants who end up in emergency rooms.

So even people in, quote, developed countries should be concerned about NCC because it has an economical impact on the country.

So for these monetary impact measures one has to be aware that uncertainty is massive as well.

All of those estimates have huge confidence intervals because we're very uncertain about all the data we put in there because of the nature of NCC. We don't know enough about it.

To conclude, I think that the burden of cysticercosis remains very poorly described. But, the little evidence we know seems to suggest that people with NCC have lower quality of life than people who do not have those symptoms. However, people with the same symptoms seem to have similar quality of life to those with NCC and the same symptoms.

Cysticercosis is associated with several millions of dollars every year in poor society. It's probably billions worldwide, but until these studies are conducted we can't tell. And the DALYs loss are probably important. But we need to improve these estimates, especially to talk with decision-makers to make them realize that it might be important to control NCC. And not only that, also to invest in better studies to see what works in proper, community-based, randomized trials so that we can really test the effectiveness of different, alternative strategies.

We still need to figure out where the endemic areas are. So even within a country, there are some patches of NCC. And we've seen that in Burkina Faso. We had a Muslim village. We did not find a single case of NCC. Whereas, in the two other villages that were non-Muslim 45% of people with epilepsy had NCC. So you can't really generalize a study in endemic areas of one country to the whole country. Then we'll overestimate the burden of NCC. And we don't want to do that.

We have to work on these other symptoms. To my knowledge, there is only been one case control study looking at NCC and stroke. There's more that needs to be done, say for depressive disorders.

We really need to improve the burden estimate to provide better evidence for better decision making to improve the health of people. And that's really the ultimate goal. We cannot take proper decisions in the absence of evidence. And we want to improve the lives of those people. And all of those symptoms are theoretically preventable.

So if we can understand this better, invest more in it, we might be able to prevent a lot of cases of epilepsy, stroke, depressive disorders, headaches in these areas of the world.

This is all I had for you. The references are on the next slide for those who are interested. If you have any questions I'm available to answer. Sorry if I went a little bit long.

Joe Perpich: This is Joe Perpich again, Dr. Carabin. So much is being done on the whole genome sequencing with a variety of parasites besides viruses, especially, obviously, malaria. What, if anything, has been done here, especially now that you can do total genomes pretty cheaply, sort of being done in this arena? If at all?

Hélène Carabin: To my knowledge, there has been one study from India where they looked at genetic differences among people that had symptoms associated with NCC and people that had NCC and no symptoms (in the brain). And they did find some genetic difference between these cases. But that's all I know that has been done on that topic.

Now, I don't know if others in the group have seen something.

But this is the only study I've seen being done on this. And indeed, that would be really interesting to see.

Are people with NCC different genetically? Is there something with different populations that, first of all, would make the cysts go to the brain? And no one knows that.

We don't even know if some people only have the cyst in the body, and if people only have it in the brain, why is that? Is there a genetic factor that explains this? That would be interesting to know, especially if we could do something about it.

I don't know if that answers your question?

Joe Perpich: It does. Thanks. Actually on the front page of New York Times today, they've done whole genome sequencing on two people who have very low cholesterol levels and three charter companies have done the total sequencing and are now making drugs that mimic that genetic profile. Just what you said about whether someone was susceptible to neurocysticercosis to others is an intriguing way of looking at.

Hélène Carabin: Yes. Another thing that I am thinking would be interesting to look at, if we could, would be the microbiome. Because they're now seeing evidence that the gut microbiome may be affected or may be talking to the brain. And this may be something a little bit easier to conduct because getting stool from people would be easier than getting blood.

There's a lot to do on this disease. There's a lot that we don't understand.

We have Ana Sanchez with a comment here. What she said it that one of the main challenges to get accurate data is the disconnect between human and veterinary health. And then she's asking if you've been able to teach some integration in countries you work in.

My answer is, at the moment, Ana, we're conducting a community-based randomized trial, testing an educational program in Burkina Faso. And the educational program includes education on both sanitation and pig management. We are measuring pig cysticercosis with antigen ELISA and human cysticercosis with antigen ELISA.

We are also trying to look at neurocysticercosis but our sample will probably not be large enough to find something significant but we might see trends with this study.

In Burkina, it works very well. But Burkina they don't have a lot of veterinarians. They don't have a school anymore. So there's very few people that can work on the agricultural sector.

Joe Perpich: Can you read the next one?

Hélène Carabin: The genomics of microbiome?

Joe Perpich: Pig vaccination?

Hélène Carabin: Yes, the pig vaccination works for pigs. There have not been any studies, to this date, of the impact of pig vaccination on human outcomes. And so far they've only randomized pigs. They have not randomized communities. And the thing is, with infectious diseases, because of transmission dynamics, the study design has to be a little bit different. If you vaccinate two pigs in a litter and leave the other two pigs unvaccinated you can have an idea of how well protected that pig is, but you don't see the big picture at the community level. So there has not been studies on the effect of pig vaccination on human cysticercosis or human NCC to this date.
I believe that the study in Peru did include an arm that included that but I'm not entirely sure. And I'm hoping we'll have results from that, from that study in Peru.

And Angelina has a very good question. How sustainable is the vaccination of pigs in a low resource setting?

I don't think it is. That's my personal opinion. Pigs are born every day. Farmers cannot always even feed themselves. I doubt very much that they would be able to pay for a vaccine, especially that it would have to be given very regularly. Even if it were during a five year duration, unless it would be huge subsidies from the government, I don't think that's very sustainable at this time.

Joel had the question regarding differentiation between human cysticercosis and brain abscesses. Radiologists-- and this is not my expertise-- but radiologists, then they see NCC with good CTs, I believe they can really make a difference especially in some cases. When you can see the scolex then it's very obvious it's NCC. When it's a calcification, it's typically quite obvious it's

NCC. To my knowledge, they can make that differentiation. Especially the more slices that CT would have the more accurate the differential diagnosis would be between these two.

Any other questions?

I thank you for being out there. And again, if any one of you have data or interest in doing something on that topic I would be very pleased to talk about it.

OK. Well, thank you all for being here. I think that will end this webinar. Please keep in touch. I hope to see you all soon.

Joe Perpich: Thank you very much, Dr. Carabin.