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[00:00:04.766]
(Patricia Thomas:) My name is Pat Thomas,
and I am the Knight Chair in Health

[00:00:08.546]
and Medical Journalism at the Grady College
of Journalism and Mass Communication.

[00:00:12.676]
And it is my pleasure to welcome all of you once
again to the Voices from the Vanguard lecture.

[00:00:18.706]
Sixteen times in the last four
years we brought before you people

[00:00:23.386]
who have a unique first hand
perspectives on the diseases

[00:00:27.596]
that affect neglected people
throughout the world.

[00:00:31.116]
We have taken them as neglected diseases
too often, but it is really about the people

[00:00:35.346]
in the final analysis and we are grateful to all
the students and faculty members who have come

[00:00:41.266]
to so many of these occasions to hear these
wonderful speakers who have joined us.

[00:00:46.826]
This is the last one for this year, but
Dan Colley, my partner in this enterprise

[00:00:52.196]
who is the Director of the Center for
Tropical and Emerging Global Diseases.

[00:00:56.356]
Professor Colley and I want
to emphasize our commitment

[00:00:59.486]
to bringing this series back next year.

[00:01:02.206]
We know there are a lot of great investigators,
people who have walked the walk as well

[00:01:08.436]

as talking the talk and we are looking forward to doing this again in 2010.

[00:01:13.496]

Tonight, we are really, really pleased to have with us Dr. Jennifer Friedman,

[00:01:17.266]

a pediatrician with a special interest in worms.

[00:01:20.366]

Well, I guess that all doctors who treat children have probably seen their share

[00:01:24.896]

of worms, but she is interested in it in a greater, more global sense.

[00:01:29.826]

I don't know how much contacts she had with worms growing up in New Jersey and I don't think

[00:01:34.996]

that Providence, Rhode Island is a particularly wormy place, so perhaps it is,

[00:01:39.356]

but she did attend Brown University and -- the Brown University School of Medicine.

[00:01:45.706]

She couldn't seem to get away from there, except when she got a Fulbright fellowship and went

[00:01:49.676]

to Africa and I think as she will tell you that changed her world because she has gone

[00:01:55.096]

on to become a preeminent young researcher in the area of helminthiasis and particularly

[00:02:01.406]

in what she calls polyparasitism,

[00:02:04.036]

the concomitant infection with more than one type of worm.

[00:02:09.626]

So, I hope there are going to be some really outstanding slides here.

[00:02:13.516]

At any rate, we are thrilled to have her with us tonight.

[00:02:17.996]

I want to remind you that following her talk, we will be adjourning to next door

[00:02:22.816]
to Demosthenian Hall where
we will have refreshments

[00:02:25.626]
and you will have a chance to talk to her.

[00:02:28.106]
So, thanks for coming, and Dr. Friedman.

[00:02:31.516]
(Applause)

[00:02:50.276]
(Dr. Jennifer Friedman:) Thank you
very much for that introduction.

[00:02:52.206]
It is really lovely to be here.

[00:02:54.186]
I am quite honored to follow in the footsteps
of the 15 other investigators and journalists

[00:03:00.206]
and scientists who have been here to date.

[00:03:02.836]
And I would like to talk to you a little
bit today about our experiences in working

[00:03:07.406]
in the Philippines, but really
more broadly on the current status

[00:03:11.346]
of geohelminths and schistosomiasis.

[00:03:15.966]
And I would like to begin by mentioning
Dr. Norman Stoll's presidential address

[00:03:22.086]
to the American Society of Tropical
Medicine and Hygiene equivalent.

[00:03:26.436]
Just after World War II when many servicemen
and women, probably more servicemen

[00:03:31.106]
at that point returned with a whole
host of different worms that many

[00:03:35.556]
of which had never been seen or
identified in this country before.

[00:03:39.986]

And it really this address
has been quoted many, many,

[00:03:44.246]
many a times in the parasitic disease literature
in which he said and declared that we live

[00:03:49.806]
in this "wormy world" and even
as recently as a few years ago,

[00:03:54.726]
reviews of this topic unfortunately state
that we are sort of in the same boat,

[00:04:01.246]
still living in quite a wormy world.

[00:04:04.136]
During his address, he mentioned that
probably 342 helminths have been associated

[00:04:09.086]
with human hosts, but about 25 of them are
of the greatest public health significance

[00:04:14.756]
and I want to remind you that today, I am
only going to talk to you about four of those

[00:04:19.106]
and the fact that many people all over
the world are co-infected with those four

[00:04:25.326]
and many, many others simultaneously.

[00:04:28.366]
I also and re-reading his address from 1947,
I wanted to take some advice and I think

[00:04:36.646]
that it is good advice for all of us to heed.

[00:04:39.366]
I think as scientists we really
live in our own sort of world.

[00:04:43.136]
Everyone has their favorite worm and he said
that each parasitologist just wants to live

[00:04:49.506]
in his thinking in one world with the
species which particularly interests him.

[00:04:53.546]
So, some progress has been
made since I am not him

[00:04:56.606]
and I am here talking to you about parasites.

[00:04:59.016]
But, I think that this is a common
theme and I think that more and more,

[00:05:04.416]
we all need especially the scientists
to recognize that we live in a world

[00:05:09.436]
with unfortunately, where
children in particular are infected

[00:05:12.556]
with many different parasites,
bacteria, viruses.

[00:05:15.976]
And that if we don't start to really
work together to combat these diseases

[00:05:20.186]
and really work in our own
labs, in our own field sites,

[00:05:24.896]
that we really won't really do our best
to decrease polyparasitism in the world.

[00:05:30.726]
So, what I would like to talk to you a little
bit about today, again really going to focus

[00:05:34.486]
on four worms, geohelminth,
the three geohelminths,

[00:05:37.386]
the main three geohelminths and schistosomiasis.

[00:05:39.646]
We will talk about the fact that it
probably is still a very wormy world

[00:05:43.736]
and some of the consequences of that.

[00:05:45.506]
We will talk a little bit about what
polyparasitism means and how we are starting

[00:05:49.606]
to think about that and measure outcomes related
to having more than one parasite or looking

[00:05:54.186]
at more than one parasite, some of
the current interventions and hurdles,

[00:05:58.416]
and hopefully, some future directions.

[00:06:00.276]
So, I wanted to start by making
this a little bit concrete for us.

[00:06:05.486]
This is a Trichuris worm which is just
barely visible to the naked eye and I would

[00:06:11.576]
like to remind us that this worm, and I
will show you the life cycle actually,

[00:06:15.396]
hundreds of these worms would infect a
given child and produce thousands of eggs

[00:06:21.336]
that then contaminate the environment.

[00:06:25.386]
So, I would like you guys to think a
little bit about a common theme as we talk

[00:06:28.656]
about life cycles here because -- the hint is
poverty and what you see with the life cycle

[00:06:36.216]
of Trichuris and also remember that
these worms are really, you know,

[00:06:40.636]
you sort of have to know thine
enemy and respect thine enemy.

[00:06:44.536]
If we are battling these worms, you really still
have to appreciate how well they are adapted

[00:06:49.546]
to human hosts, how they are adapted to their
and our environment, and how that makes it very,

[00:06:55.836]
very difficult to stop the transmission cycles.

[00:06:58.906]
So, this worm actually, the eggs are ingested.

[00:07:01.306]
It actually leaves -- sorry, this worm
actually stays in the colon and multiplies

[00:07:06.506]
and within a few months of infecting,
the adult female worm starts making eggs

[00:07:11.986]
that then contaminate the environment.

[00:07:14.586]
And this worm has been associated
with malnutrition

[00:07:18.106]
and its severe form a dysentery syndrome
where kids have bloody stools and diarrhea

[00:07:23.296]
and more severe malnutrition
and anemia along with it.

[00:07:28.516]
Another worm I would like to talk
to you about is *Ascaris lumbricoides*

[00:07:32.586]
and *Ascaris* has another interesting life cycle.

[00:07:36.196]
Ascaris actually gets ingested.

[00:07:38.696]
So, basically eggs are contaminating
the environment

[00:07:42.196]
and basically fecally contaminated
environment where eggs pass out through feces

[00:07:46.756]
and then are basically ingested by human host
after a period of development in soil usually.

[00:07:53.406]
And then they actually leave the gut and have
a whole migration through your body that ends

[00:07:59.366]
up back in your lungs and causes an irritant
cough so that you then cough up the larva,

[00:08:05.326]
swallow it again and it ends
up back in your intestine

[00:08:08.936]
and this worm is called the giant
roundworm and we'll show you why that is.

[00:08:13.786]
And again, this is just one worm and
children can have hundreds of these worms.

[00:08:18.616]
So, this is a collection of worms of this.

[00:08:21.856]

This is Ascaris.

[00:08:22.716]

It looks like rubber bands, but that is Ascaris lumbricoides that were collected during a day

[00:08:26.566]

of treatment in a Bangladesh village.

[00:08:29.086]

It is also important to remember that when we are talking about interventions

[00:08:33.246]

for these diseases that this is a big issue, right, because there are many people who,

[00:08:37.776]

especially when you are talking about treating kids that have high parasite densities

[00:08:42.166]

and you treat someone and all of a sudden, the worms --

[00:08:44.886]

basically, stops the worm from being able to contract their muscles and swim and stay

[00:08:49.366]

in the intestine, all of a sudden they are passed in the stool.

[00:08:52.796]

And it is a very alarming thing and a lot of people who don't think about that

[00:08:57.016]

or talk to people that know the local populations a little bit better find the

[00:09:02.006]

compliance is not as good as they expect.

[00:09:04.946]

So, this is a child, so you can imagine the child that has such a large worm

[00:09:09.126]

at a very intense infection can have a lot of abdominal bloating, satiety.

[00:09:15.566]

We'll talk a little bit about how these worms probably cause malnutrition.

[00:09:20.036]

But basically, this is a child with

very bad *Ascaris lumbricoides* infection.

[00:09:26.136]

All right, hookworm and hookworm, I think has really always risen to its own sort of stature

[00:09:35.406]

in the United States and worldwide partly

[00:09:38.716]

because from a very early stage has been very closely associated with anemia.

[00:09:44.356]

And it got a lot of publicity even in the United States at the turn of the 20th Century

[00:09:50.686]

when the Rockefeller Sanitation Commission was out to convince Congress

[00:09:56.006]

that hookworm was holding back the South in terms of its economic development

[00:10:00.236]

and that hookworm had to be obliterated from the country if the South was to progress.

[00:10:06.226]

And this is really the kind of language that was used given the concern

[00:10:10.076]

that with the anemia associated with hookworm that work capacities would go down,

[00:10:14.956]

that people with iron deficiency anemia that that might affect their ability to think

[00:10:19.076]

and learn, and so, this worm has always gotten a lot more attention globally.

[00:10:24.916]

And hookworm also has a very interesting life cycle and is very well adapted to human host

[00:10:30.236]

who walk around with no shoes on.

[00:10:32.686]

So, when you step on the egg that has come out again in feces and is embryonating in the soil,

[00:10:39.656]

the larvae actually walk up to the highest point they can find.

[00:10:44.336]

So, usually a blade of grass waiting for the innocent, unshod child to step on it

[00:10:50.726]

and then enter your bloodstream and have a similar course to the lungs with coughing

[00:10:55.716]

and then back down into the small intestine where they ultimately reside.

[00:11:01.346]

And also, it can be fairly bulky, but most of the pathogenesis of this worm is really related

[00:11:08.756]

to anemia and bleeding through the gut.

[00:11:12.446]

So, this is an adult worm.

[00:11:14.106]

This is a single adult worm and it basically latches on to the wall of your gut

[00:11:19.706]

and it is not just the sort of mechanical force of this nasty-looking mouth,

[00:11:26.276]

but also the worm releases powerful anticoagulants, so blood thinners.

[00:11:32.916]

So, in seeding in your gut actually, it basically thins the blood along the wall here

[00:11:39.356]

and so you basically, on a very daily basis, have blood loss in the stool

[00:11:46.386]

and that is most likely the predominant cause of anemia in hookworm.

[00:11:51.916]

I should also mention that all three of the worms that we just talked

[00:11:55.276]

about are fairly good -- there is excellent therapy for them.

[00:11:58.826]

You use Albendazole.

[00:12:01.006]

A single dose has very good efficacy.

[00:12:03.676]

It is even better with two doses likely

[00:12:06.166]

with almost 100 percent clearance
of most of these worms.

[00:12:09.166]

So, a single dose often clears these
infections, but if you treat them in school

[00:12:13.856]

and they walk home without
shoes on, what happens?

[00:12:17.126]

Right, they are immediately re-infected.

[00:12:20.226]

So, we have very good chemotherapeutic
agents to treat geohelminths.

[00:12:24.366]

That is really not the problem.

[00:12:26.536]

So, the real problem is how to deliver them,
how frequently, is that really the best,

[00:12:31.766]

most cost-effective approach or other approaches
that we will talk about a little bit better.

[00:12:36.736]

Okay, the last worm that I am going to mention
today is not technically a geohelminth.

[00:12:41.046]

It is just a helminth because it doesn't
have the soil component to its life cycle,

[00:12:46.096]

but also a very crafty worm, also depends

[00:12:49.136]

on humans either defecating or
urinating now in freshwater.

[00:12:53.326]

It has an intermediate host which is a snail.

[00:12:55.896]

So, part of its life cycle
actually occurs in a snail.

[00:13:00.226]

The second part of this life cycle is the
cercaria is released and actually swims

[00:13:06.696]

to the definitive host which is humans and then migrates to a long stage all the way

[00:13:12.946]
to either the blood vessels around the liver for two of the species or around the bladder

[00:13:18.926]
for haematobium which is a urine species.

[00:13:21.926]
So, the eggs are then deposited and cause a significant pathology around the liver

[00:13:27.156]
and then most of the eggs actually track through your body, through your bloodstream

[00:13:32.006]
down into the gut and come out again into the environment

[00:13:36.726]
when a definitive human host defecates in freshwater.

[00:13:41.756]
Okay, in case you haven't recognized the common theme here,

[00:13:48.456]
it is sanitation, sanitation and sanitation.

[00:13:51.696]
And I should also mention that what's very important --

[00:13:56.136]
this happens to be a map of the schisto endemic areas of the world.

[00:14:00.996]
But, I could show you the same map, hookworm, Ascaris and Trichuris almost exactly,

[00:14:08.276]
with a few exceptions and they would overlie in the same exact regions

[00:14:13.166]
with Sub-Saharan Africa really bearing the brunt of disease,

[00:14:17.456]
some South America still and a lot in Asia.

[00:14:20.636]
Now, figuring that I am only here talking to you about helminths today and I said we all need

[00:14:27.836]

to work together and not just think about our own pet parasite, right?

[00:14:31.616]

So, also overlay malaria and you will have a very similar look here

[00:14:37.006]

in Africa and still large parts of Asia.

[00:14:41.246]

And then, if you add in the latest scourge of HIV to this,

[00:14:45.606]

the distribution looks very similar.

[00:14:47.906]

So again, these are all diseases of poverty and much what we can --

[00:14:53.276]

we can come a very long way with economic development, sanitation, water and hygiene

[00:14:59.086]

and it may not be that chemotherapeutic cures are the only way to go here.

[00:15:05.246]

So, this is a child with advanced hepatic schistosomiasis.

[00:15:08.956]

So, what you see here is -- what's really quite amazing

[00:15:12.456]

about schisto worms are they actually sit in your bloodstream.

[00:15:16.126]

So, most of us know that our bloodstream is about the most sterile part of our body

[00:15:22.686]

and the human host does not do well with circulating pathogens in the bloodstream.

[00:15:28.696]

But, this worm has done such a good job of evading itself mostly by cloaking itself

[00:15:35.746]

with human antigens so that to a human host, for all the world looks like a self-antigen

[00:15:42.306]

and so much less immunogenic,

and it sits right there

[00:15:45.386]
in the bloodstream making
thousands of eggs a day.

[00:15:50.826]
Everyone's favorite story about schistosomes
is that they live in permanent copulation,

[00:15:55.716]
so the man and the woman live in permanent
copulation in the liver, bloodstream,

[00:16:01.766]
or for the urinary species in the bladder
plexus and produce thousands of eggs

[00:16:09.616]
which are what produces this --
mostly what produces pathology.

[00:16:12.476]
Some of those eggs are swept upstream
and cause really terrible liver fibrosis.

[00:16:16.936]
So, these kids really look and act like
an adult with really horrific hepatitis C

[00:16:22.676]
or B with cirrhosis of the liver or cirrhosis
of the liver due to alcoholic cirrhosis.

[00:16:30.336]
And so, this is a morbidity related to
schisto that is fatal and not what we call one

[00:16:36.576]
of the more subtle morbidities
which is how often people talk

[00:16:40.146]
about helminth infections that they are there.

[00:16:42.386]
We sort of co-exist with them and
they cause some subtle morbidities

[00:16:45.446]
and we will talk a little bit about what some
of those subtle morbidities are and whether

[00:16:48.776]
or not they are really all that subtle.

[00:16:50.546]
I should also point out a syndrome
called schistosomal dwarfism.

[00:16:54.166]

So, this is actually not a child.

[00:16:57.266]

This is someone who is about 16 years old and it is a very profound

[00:17:02.106]

with syndrome called schistosomal dwarfism.

[00:17:05.056]

Not the best term, but the kids with very bad liver disease

[00:17:09.726]

with schisto have really terrible stunting of their growth,

[00:17:12.896]

probably for a lot of different biologic reasons.

[00:17:15.666]

But, this is an example of the growth stunting and they enter puberty or 20 years old

[00:17:20.876]

and have really only achieved heights on average of about four to four and a half feet.

[00:17:27.936]

So, how would worms that live in your gut or worm that lives

[00:17:31.686]

in your bloodstream cause undernutrition?

[00:17:35.186]

And then, we will talk a little bit why we care so much about undernutrition.

[00:17:38.626]

A lot of these worms, we think particularly schisto which sits again right in the middle

[00:17:44.876]

of your bloodstream and makes lots of eggs that are very immunogenic,

[00:17:49.466]

we found that they make a lot of these cytokines.

[00:17:51.996]

These cytokines are considered the cause of host of different bacterial,

[00:17:57.596]

viral and parasitic infections and the host of (inaudible) season response.

[00:18:03.476]

These are very known modulators of cachexia or anorexia which cause very decreased appetite.

[00:18:11.286]

So, even if food is available in this context, kids have much decreased appetite

[00:18:15.836]

and also alters muscle metabolism so that you have muscle wasting and loss

[00:18:21.216]

of important proteins and muscle mass in the urine.

[00:18:24.896]

As you saw, these worms can be very bulky and a lot of them cause -- people report pain, nausea,

[00:18:33.896]

vomiting, early satiety, and that itself may cause decreased intake which may be related

[00:18:39.616]

to the malnutrition we know the worms caused.

[00:18:42.936]

And the worm bulk itself, so particularly with *Ascaris*, the giant roundworm probably leads

[00:18:49.696]

to some malabsorption if the worm really blocks the host's ability to absorb nutrients

[00:18:55.876]

which are then lost in the feces.

[00:19:00.016]

So, these are some of the ways we think that worms --

[00:19:02.996]

so all of these worms have been implicated in undernutrition particularly

[00:19:07.056]

at higher intensities of infection and these are some of the ways that that is likely happening.

[00:19:14.456]

So, I am going to show you a little bit of our data from a study site in the Philippines

[00:19:20.976]

where we treated kids for schisto, just schisto and then look at what happened

[00:19:26.326]

to their nutritional status after
we treated them with Praziquantel,

[00:19:30.436]
a drug of choice of schisto over 18 months.

[00:19:33.456]
And so, a BMI Z-score is a really nice way
of assessing overall macronutrient status

[00:19:40.006]
of a child and one thing you will notice
is that overall, we treated everybody

[00:19:48.006]
and everybody had a positive inflection here.

[00:19:51.496]
So, one thing I would say is a BMI Z-score --
a Z-score standardizes a nutritional status

[00:19:58.936]
to zero, so it is really a standard -- think
of it as a standard deviation from a mean.

[00:20:03.716]
So, your BMI Z-score, if it is 1; it means it
is 1 standard deviation away from a healthy,

[00:20:12.496]
happens to be American farm-fed
boy or girl of that same age.

[00:20:19.636]
So, if you have a -- overall,
if your BMI Z-score was minus 1,

[00:20:25.606]
you are about minus 1 standard
deviation lower from the mean

[00:20:30.116]
of the healthy reference population of a
similarly age and gender matched child.

[00:20:36.506]
These are now showing you a change
in BMI Z-score after we treat you.

[00:20:40.316]
If you had gone to this village and not
treated people, for the most part overtime

[00:20:45.796]
as kids get older in this age range,

[00:20:48.636]
they were about 7 to 18 years old you would
have watched their BMI Z-score fall overtime

[00:20:55.116]
because you leave kids in an environment that
is not healthy over the years without treatment.

[00:20:59.786]
Overall, they really fall off
in terms of their nutrition.

[00:21:03.376]
When you are comparing them to --

[00:21:04.666]
they are basically competing with healthy
American kids when you compare them this way.

[00:21:08.336]
And we can talk a little bit
after about the pros and cons

[00:21:11.186]
of using a healthy American reference standard.

[00:21:14.186]
But, that is what we do, that is what
the WHO and CDC recommends for a lot

[00:21:18.426]
of different complicated baseline.

[00:21:20.396]
But, basically what you see what happens is that
overall, this is your change in BMI Z-score,

[00:21:26.546]
if you were wasted at the
beginning of the study, overall,

[00:21:30.616]
your change from baseline was much
greater than if you were not wasted.

[00:21:35.396]
But overall, everybody had a positive
inflection and this is a phenomenon

[00:21:40.646]
that is found all over the world.

[00:21:42.146]
So, kids who are doing worse on a lot of
different measures, when you treat them

[00:21:47.596]
for one illness, have a much
better rebound effect.

[00:21:51.466]
And that may very well be because these
were kids that were suffering more.

[00:21:55.076]

There is a lot of variability in terms of host immune responses to schisto,

[00:21:59.826]

how much morbidity each host suffers so that this group may very well have been the kids

[00:22:04.856]

that were much worse off from their schisto for whatever immunologic or other reasons

[00:22:10.986]

and you liberate them from that disease

[00:22:12.856]

and you basically watch their BMI Z-score go up overtime.

[00:22:18.916]

This is a similar idea except here we are looking at treatment and your linear growth here

[00:22:25.676]

and then your weight gain from baseline here and a group of kids that we watched for 18 months

[00:22:31.076]

and this is their re-infection status at 18 months.

[00:22:33.866]

So, either they were not re-infected at all, uninfected.

[00:22:36.966]

They got re-infected, but in a low intensity, moderate or high and then,

[00:22:40.946]

the same thing for their weight gain from baseline.

[00:22:43.786]

So obviously, everybody is going to grow a certain number of centimeters.

[00:22:46.666]

This is all positive and what you notice is that the low intensity re-infection,

[00:22:50.786]

they didn't really affect their linear growth very much at 18 months,

[00:22:54.586]

but when you get out to the moderate and the higher intensity re-infection,

[00:22:57.876]

these kids really had some growth
stunting from their re-infection

[00:23:01.736]
and the same was true for their weight gain.

[00:23:03.656]
Low intensity re-infection, not so bad.

[00:23:05.676]
And then, if you get re-infected
at higher intensities,

[00:23:09.666]
your weight gain from baseline is significantly
different than the group that gets uninfected.

[00:23:15.286]
And to remind you again, all we did was
treat them for one worm with this standpoint

[00:23:20.086]
and so this is sort of the power
of one worm in terms of its impact

[00:23:23.786]
on nutritional status knowing that these are
kids that I can tell you harbored almost all

[00:23:29.596]
of the geohelminths at low
to high intensity range.

[00:23:34.096]
So why do -- you probably have
heard in public health courses

[00:23:39.246]
and undergraduate courses the importance of
malnutrition and nutrition to child health.

[00:23:45.956]
This is really considered one of the most
important metrics of child health and even

[00:23:52.076]
as a mere for the health of a society.

[00:23:56.596]
So, the prevalence of undernutrition in a
community can give you a lot of information

[00:24:02.126]
about the overall health of that community and
there are a lot of different reasons for that.

[00:24:07.616]
One being protein energy
malnutrition itself kills children.

[00:24:12.256]

So, many children, millions
of children each year die

[00:24:16.066]

from food scarcity and protein
energy malnutrition.

[00:24:19.496]

Having protein energy malnutrition
places children under 5 at increased risk

[00:24:25.426]

for mortality from any cause however.

[00:24:28.626]

An estimate -- there is a very elegant
article by Pelletier that looks at trying

[00:24:34.816]

to estimate the number of deaths that are
attributable to the potentiating effects

[00:24:40.786]

of malnutrition and he actually
estimated that that is about 56 percent

[00:24:46.226]

of child deaths maybe preventable if that
child was not malnourished when they were hit

[00:24:52.126]

with whatever the ultimate
cause of their death was.

[00:24:55.876]

So, I'll give you a very good
example from a malaria study.

[00:24:58.936]

When you give children bed
nets for malaria prevention,

[00:25:03.116]

you do a pretty good job preventing their
malaria-related morbidity and mortality.

[00:25:07.246]

But, more than one study found that you
also reduce the risk of dying from measles.

[00:25:13.016]

So, measles is a nice indicator because
it is not like a lot of other diseases.

[00:25:16.976]

It wasn't malaria and they just had, you know,

[00:25:19.846]

diarrhea or was it true gastroenteritis

that really killed the child.

[00:25:25.206]

Measles is measles and bed nets reduce your mortality from measles and why is that?

[00:25:31.376]

Probably, because if you control someone's malaria, you are probably making that child

[00:25:38.346]

that much more robust in every way and most importantly,

[00:25:42.256]

probably you are reducing their acute and chronic anemia

[00:25:45.346]

and you are reducing their undernutrition so then when they get hit with measles,

[00:25:50.126]

they are better able to survive that next insult.

[00:25:54.156]

That has also been found for gastrointestinal diseases.

[00:25:57.646]

So, deaths from severe diarrhea or dysentery also less in children that are not malnourished

[00:26:05.186]

at the time they get that illness.

[00:26:07.546]

And given most kids in the world actually have mild to moderate malnutrition,

[00:26:12.846]

that created burden in terms of numbers and prevalence is in the mild to moderate.

[00:26:17.866]

So, if you can improve the nutritional status of kids and move them out of this range

[00:26:23.366]

or even out of this range into well-nourished kids, when they ultimately get their measles

[00:26:29.096]

or their malaria or their bad gastroenteritis,

[00:26:32.546]

they may very well be more likely to survive that.

[00:26:35.226]

And, it is one of the reasons we think that when people talk about subtle morbidities

[00:26:39.056]

of helminth infection, so the idea that, yeah,

[00:26:42.256]

kids co-exist with multiple helminth infections and isn't that okay.

[00:26:46.716]

The parasite is sort of adapted to live with us for years and years.

[00:26:51.066]

I am not sure that it is really okay.

[00:26:52.566]

If we know that each worm is causing at least some malnutrition and that malnutrition

[00:26:59.006]

in turn places them at greater risk of death, I think that it is one of the real arguments

[00:27:04.096]

that the very least that we keep intensities of infection lower, we may do a lot in terms

[00:27:11.086]

of decreasing particularly child mortality.

[00:27:15.016]

Also, malnutrition has been associated with poor cognitive performance and concentration

[00:27:20.656]

and really may limit kids who are already very limited opportunities to take advantage

[00:27:25.946]

of education in lesser developed countries.

[00:27:28.576]

And stunting, we always talk about as being related to decreased adult work capacity

[00:27:33.736]

for a nation and also, places pregnant women at greater risk for adverse birth outcomes.

[00:27:39.996]

So, this is a quick look.

[00:27:41.576]

Now, I want to focus -- change gears a little bit and talk about anemia.

[00:27:45.876]

So, most of us understand that anemia is not good for us for a whole host

[00:27:49.816]
of different reasons ranging from probably not good for our energy level

[00:27:55.436]
or oxygen carrying capacity or work capacity.

[00:27:58.156]
In children in particular, we know that iron deficiency anemia in particular is not good

[00:28:02.416]
for your cognitive function and severe iron deficiency anemia also not good for your growth.

[00:28:08.476]
So, this is a look at, again, S. japonicum infection and so here,

[00:28:13.266]
I can be faulted for separating out the worms, but we were sort of interested

[00:28:17.776]
in getting a sense of the burden that each of these worms and then,

[00:28:20.366]
I will show you some data from the polyparasitic work.

[00:28:23.656]
But here, you can see, if you have heavy intensity S. japonicum,

[00:28:27.956]
you have a significantly lower adjusted hemoglobin.

[00:28:31.436]
Now, if you look at just hookworm infection, moderate or heavy infection,

[00:28:35.726]
significantly lower hemoglobin and same for Trichuris.

[00:28:38.796]
All of these analyses are adjusted for socioeconomic status and age and gender

[00:28:46.306]
because you could argue back to me very easily that all

[00:28:48.746]
of these are factors that move at poverty.

[00:28:51.646]

So, I am telling you that I think it is this, this is cross-sectional data,

[00:28:56.006]

and you may say to me, it is not that they have schisto at this intensity.

[00:28:59.536]

It is that they are poor and they are poor, so they are in the rice paddies,

[00:29:03.266]

going in freshwater, getting infected with schisto all the time instead of being in school.

[00:29:07.646]

So, we really do our best here to try as much as you can control for known compounders to try

[00:29:14.056]

to really adjust for those and as you might expect, as yes, maternal education --

[00:29:18.426]

socioeconomic status, maternal education

[00:29:20.816]

in particular were all very highly related to a child's hemoglobin as well.

[00:29:26.526]

So hopefully, we're giving you a good sense of what the worm itself does.

[00:29:30.146]

And again, I am showing you each of this separately.

[00:29:32.486]

Now, think about the fact that most of these kids are polyparasitized,

[00:29:36.276]

so they don't just have one worm.

[00:29:38.106]

They have at least two or more of them in most endemic areas.

[00:29:42.576]

Here is a look again at a sort of dose response by hemoglobin by intensity

[00:29:47.536]

of *S. japonicum* infection and you can see the uninfected group with a nice,

[00:29:52.036]

juicy hemoglobin of close to 13 all the way

[00:29:54.576]

down to the more intensity infected
group of eleven and a half or so.

[00:30:00.296]

Again, all adjusted for the other worms
and socioeconomic status in particular.

[00:30:05.006]

All right, and then, one final data slide,
I think here to look at what happens

[00:30:11.926]

if we treated you for your schisto with
Praziquantel and then we basically look

[00:30:17.266]

at what happen overtime if
you are re-infected or not.

[00:30:21.146]

So, in the red, you have the group
that remained uninfected, and so,

[00:30:24.116]

this is a change from baseline,
so everyone starts at about zero

[00:30:27.436]

and if you were re-infected overtime, your
hemoglobin stays below and at the very end

[00:30:34.406]

of 18 months was significantly lower than zero,

[00:30:37.306]

meaning that you had a significant
drop in your hemoglobin.

[00:30:40.056]

Whereas, the group that stayed
uninfected stays above that zero line,

[00:30:43.546]

meaning that they did not have
a drop in their hemoglobin.

[00:30:46.396]

Okay, as we have mentioned now, most of
the world's children don't have just one

[00:30:53.956]

of the parasites that we talked about.

[00:30:56.136]

If you look at the map that I showed you, in
most part of the world, most kids have two

[00:31:01.846]

or more of these parasites and some have all four or three of them.

[00:31:06.026]

The other hard part is that many of them have them in varying degrees of intensity

[00:31:10.256]

of infection and as I showed you, at least with schisto, if any other worms to a lesser extent,

[00:31:15.586]

it is probably very important the intensity of each infection that you have.

[00:31:19.966]

But, what happens now if you combine the data and look at the worms across low intensity even

[00:31:28.016]

because the lower has always been, even from WHO, that well,

[00:31:31.566]

low intensity parasitic infections don't even cause low grade morbidity.

[00:31:36.196]

They probably don't cause much malnutrition, probably don't cause much anemia.

[00:31:39.626]

So, that is nice if you live in an area where you just have one worm

[00:31:43.726]

at low intensity infection, but as we said, most of these kids have multiple infections.

[00:31:50.256]

And a very nice study done by Dr. Izzia Mamah (assumed spelling) who is a PhD student

[00:31:55.386]

that worked with us and was very interested in this phenomenon said, "I am going to look

[00:31:59.146]

at all the kids who have low intensity infections.

[00:32:02.546]

I am going to group them in one group, and I am going to compare them to a reference group

[00:32:06.236]

that had no infections or even just one low intensity," And the kids

[00:32:10.456]
that had multiple infections even all at
lower intensity had much higher morbidity

[00:32:18.666]
than you would have even seen if
they had one at a high intensity.

[00:32:22.136]
So, these kids acted like they were
these -- a child who had, for example,

[00:32:26.116]
a very high intensity single schisto infection.

[00:32:28.996]
Then, when you got into the kids that had
higher intensity, multiple infections,

[00:32:33.606]
these kids really, really, really
look sick with hemoglobin on average

[00:32:38.736]
of about 2 grams per deciliter
lower than that reference group

[00:32:41.656]
of uninfected or one low intensity infection.

[00:32:44.296]
The problem actually was you couldn't
find enough kids for the reference group

[00:32:47.556]
that had no infections so she included the low
intensity in her reference group which means

[00:32:52.416]
that probably the difference is even
a little bit stronger than that.

[00:32:56.916]
So, even if you had two or more low intensity
infections compared to uninfected or one,

[00:33:01.946]
you had five times the chance of having anemia.

[00:33:06.116]
And then, she also got into
some interesting work on synergy

[00:33:09.406]
which is a very complicated topic.

[00:33:11.486]
But basically, what she found was having more
than one worm may not necessarily be additive.

[00:33:18.506]

So, it may not be that hookworm plus
Ascaris equals two dollars of anemia.

[00:33:26.736]

It is probably much more complicated than
that such that there is a lot of concern

[00:33:30.416]

that having two worms makes you look
much worse than just having two worms

[00:33:35.186]

that they might have some negative synergistic
effects that make that anemia worse.

[00:33:40.006]

All right, so how do you tackle this problem?

[00:33:44.236]

So, I am showing you a mud hut
for a few different reasons.

[00:33:48.956]

As all of you guys can see very
clearly, there is no electricity here.

[00:33:54.326]

I can also tell you there is
no long-drop latrine here.

[00:33:57.966]

There are no hidden pipes with freshwater going
into this house, and as I mentioned to you,

[00:34:04.476]

these worms have adapted over thousands of
years to the human host to know how we live

[00:34:11.036]

in resource-poor settings and
how to take advantage of that.

[00:34:14.866]

So, there is no running water in there.

[00:34:16.696]

There is no American standard porcelain
bathroom in there, and there is not even

[00:34:22.096]

in this particular context a long-drop.

[00:34:24.726]

Because I think the theme overall
is that for helminth infections,

[00:34:28.756]

if you can keep human feces
contained and away from humans,

[00:34:32.506]
you will go a huge way to decrease transmission.

[00:34:36.526]
So, we recognized this in early 1920's as I mentioned, the Rockefeller Sanitary Commission

[00:34:44.506]
to report to Congress and they designed these to distribute all over the United States

[00:34:51.556]
and this is how they picked their design in part.

[00:34:54.786]
They knew that hookworm larvae crawled 4 feet.

[00:34:57.686]
The impetus for distributing these was to try to decrease hookworm infection in the United States

[00:35:04.166]
and so, they built it 6 feet deep and it was actually a very effective intervention

[00:35:10.876]
at reducing hookworm in the States.

[00:35:15.026]
So this, however, is the reality in many parts of Africa and I don't mean this at all

[00:35:20.756]
to be degrading, but this is sort of the reality.

[00:35:23.706]
I actually think these two are very cute.

[00:35:25.646]
They are sharing a little bit of ugali and some bean mix,

[00:35:29.416]
but the environment is completely fecally contaminated.

[00:35:33.726]
If you don't have a long-drop, this is where kids go, parents send to go or going outside

[00:35:39.776]
to go either just outside in the back of a house.

[00:35:44.346]
If they live near water source, that is commonly where people go

[00:35:47.936]

which is then very bad for
schisto transmission, right?

[00:35:52.466]

Night soil is another still
very commonly used fertilizer.

[00:35:57.016]

Does everyone know what night soil is?

[00:35:59.106]

So, night soil is when you take --
used as fertilizer often a mix of human

[00:36:04.206]

and domesticated animal feces to fertilize soil.

[00:36:09.616]

It is apparently actually a
very most excellent fertilizer,

[00:36:13.096]

but not good for the environment
in terms of helminth infections.

[00:36:18.406]

And then, water.

[00:36:20.416]

We would go a very long way also
in terms of hygiene and health

[00:36:24.136]

if we could have better water
supplies for families.

[00:36:27.886]

A lot of students asked me, well you know,
how about you just have a potty for everybody

[00:36:32.536]

and everybody washes their hands after they
go and the truth is if you have walked miles

[00:36:37.816]

of this much water on your head and you are
picking out this water that doesn't even look

[00:36:41.296]

so clean, you probably don't have a lot
leftover to either wash your dishes,

[00:36:46.676]

so you don't have to go into contaminated
Lake Victoria or other sources with schisto

[00:36:52.776]

and you probably aren't going to use a

lot of your water for hand hygiene either.

[00:36:59.346]
Again, people need to wash their
clothes, wash their dishes, go for a swim

[00:37:03.916]
and these are very common gathering
places and they are very --

[00:37:07.086]
for the schisto transmission cycle as you
can imagine, this is a disaster, right?

[00:37:11.376]
This is just sort of a Cercariae-feeding frenzy.

[00:37:14.646]
This is a lovely habitat for the snails.

[00:37:18.456]
People wade in here and they get infected.

[00:37:20.956]
Many people use this as a place
to go to the bathroom and so,

[00:37:25.326]
the transmission cycle continues.

[00:37:28.196]
And in studies all over the world of schisto,
it is always these young teenage boys

[00:37:34.806]
who have the highest intensity of
infections in almost every part of the world.

[00:37:38.816]
And a lot of people think that it is the --
that young boys, I would say go for a nice swim

[00:37:43.616]
in the lake and spend hours
getting themselves re-infected.

[00:37:46.526]
In Egypt apparently where they have
urinary schisto where the eggs pass

[00:37:51.356]
out through your urine and
blood goes along with it.

[00:37:53.506]
It is a sign that you have reached manhood
when you pass your first bloody urine.

[00:37:58.466]
So, it is really sort of this schisto and

these worms are really a very much a part

[00:38:03.286]
of the everyday fabric of life and it is
not to say that people don't recognize

[00:38:07.636]
that they are important,
but this is a huge problem.

[00:38:11.766]
And the interventions and our
armamentaria are a little bit limited

[00:38:21.196]
and they are limited for a
lot of different reasons.

[00:38:24.696]
So, snails -- so people have talked about
for schisto can you really get rid of snails?

[00:38:30.266]
And, getting rid of snails as you might
imagine as we found out when you try to get rid

[00:38:35.256]
of mosquitoes does really
horrific things to your ecosystem

[00:38:38.736]
and it is truly an insurmountable task.

[00:38:41.766]
General Mao apparently dispatched thousands
of Chinese peasants to de-snail a lot

[00:38:48.576]
of the Yangtze and Yellow
River valleys and years later,

[00:38:52.626]
he claimed that he had eradicated schisto,
which we of course know is not true

[00:38:55.856]
since they still have many
schisto-endemic regions of China.

[00:39:00.716]
Dams, creation of new dams has led to
a whole new areas endemic for schisto

[00:39:10.006]
because now you have a collection of freshwater
and the transmission cycle begins again.

[00:39:15.676]
A lot of the newer studies have looked
at school-based antihelminthic therapy

[00:39:21.306]
and this is really a very exciting -- an
exciting approach in the sense that a lot

[00:39:27.246]
of the burden of disease is borne by children.

[00:39:29.756]
They are also major reservoirs
for the environment

[00:39:32.966]
so they go home and contaminate the environment.

[00:39:35.506]
So, targeting kids in school has become
very attractive and there is a lot

[00:39:39.606]
of very interesting modeling of
prevalence of infections in schools

[00:39:43.376]
and how frequently we need to treat kids.

[00:39:45.666]
Dr. Colley's supported grant will hopefully help
to answer a lot of these for schistosomiasis,

[00:39:51.956]
how frequently do you have to go to
school and treat based on prevalence,

[00:39:54.896]
is that really an effective
intervention, is it culturally appropriate

[00:39:59.386]
and acceptable to different communities.

[00:40:03.776]
Education, so hand hygiene, sanitation
again, shoes, which goes under a category

[00:40:11.116]
of both economic development and education.

[00:40:16.616]
And then again, I think we all
really, scientists in particular

[00:40:21.786]
and public health strategists must think both
in a multidisciplinary way and across parasites.

[00:40:31.166]
So, we all have our favorite parasite.

[00:40:33.026]

NIH has taught all of us that the way you keep getting money is that you study one thing

[00:40:38.746]
into the greatest depth and you are the world's expert in this parasite, but I think I would

[00:40:44.846]
like that we are just all not to lose sight of the fact

[00:40:47.356]
that these parasites happen in a much greater context.

[00:40:51.736]
We didn't talk about malaria, HIV, filaria today, all whole host of other insults

[00:40:57.906]
to children and particularly children and pregnant women.

[00:41:00.906]
We didn't even talk about nutrition as an intervention that we have to think about

[00:41:06.956]
and iron, this has come up recently in the context of malaria.

[00:41:12.326]
So, people that are interested in giving iron to pregnant women

[00:41:15.526]
because they have studied pregnancy and that is good for birth outcomes

[00:41:18.406]
and we think in developed countries.

[00:41:22.306]
So, probably we should go and do that in lesser developed countries and it turns

[00:41:28.326]
out that this has raised a specter the malaria parasite may very well do much better

[00:41:33.786]
if you give the human host some iron to help it grow.

[00:41:36.926]
So, we have to be very careful, talk to each other,

[00:41:40.536]
and really think about these interventions that,

you know, if the geohelminth people are going

[00:41:48.046]

to the school to give the Albendazole,

[00:41:50.806]

what a good idea to have Dr. Colley's core team also know how much Praziquantel to give them

[00:41:56.666]

and at what frequency for their schistosomiasis.

[00:41:59.626]

So, we started by talking in the post World War II era a little bit and Dr. Stoll's speech

[00:42:08.996]

and it is interesting, people talk a lot

[00:42:11.466]

about the way parasites influenced history and the world.

[00:42:15.166]

And there is a very interesting history of parasitology where there are lots of theories

[00:42:21.946]

that Chairman Mao may have very well invaded Taiwan right after World War II,

[00:42:27.786]

but was halted at the Yangtze River Valley

[00:42:31.276]

when his own troops got the acute form of schistosomiasis.

[00:42:34.816]

So, Katayama fever is something that many of our troops got

[00:42:38.336]

in the Pacific rim during World War II which is a disease

[00:42:41.526]

that basically happens probably the first time

[00:42:43.786]

or in a schisto naive host gets schisto infection for the first time.

[00:42:48.856]

So, his troops basically entered the river, probably, scores of them got Katayama fever

[00:42:53.386]

and were unable to advance on Taiwan.

[00:42:56.046]

And there was pretty good evidence that that was the case.

[00:43:00.476]

But, I think more importantly, the burden of disease really rest squarely with children

[00:43:06.756]

in lesser developed countries and pregnant women and unfortunately, it is still a wormy world.

[00:43:14.116]

That said I think that we all have a lot to contribute and I think that Dr. Colley

[00:43:21.146]

and I were talking today about really young people have to get involved with global health.

[00:43:26.576]

We need fresh perspectives.

[00:43:28.166]

I started by telling you about a speech from 1947 or '49 where we were declared to live

[00:43:34.786]

in a wormy world and we all need to work together to combat the problem

[00:43:38.676]

and we still live in quite a wormy world.

[00:43:41.066]

And we made some progress, but there is lots of progress to be made and I think young people

[00:43:47.006]

who can get the skills in education, in economic development, in journalism,

[00:43:52.036]

in media can really take us a long way to combating this problem because unfortunately,

[00:43:58.316]

we do still have a long way to go.

[00:44:02.076]

And as always, we would like to thank our field staff in the Philippines for their hard work.

[00:44:06.046]

A lot of this work was done with the Research Institute of Tropical Medicine in Manila

[00:44:10.946]

and as always we thank our study subjects.

[00:44:15.956]
Thank you.

[00:44:18.516]
(Applause)

[00:44:33.710]

[00:44:34.210]