“What kind of mapping and surveillance tools should be used in low SCH transmission areas?
&
Is there enough evidence to do recommendations?”

Schistosomiasis Regional Meeting

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How I think about the transition from a control program to an elimination program, based on the goal and the starting prevalence

Morbidity Control		Elimination	
Gaining	Sustaining	(As a Public Health Problem)	0% Transmission
100%-----25%	24%---------10%[----6%]	5%----------1%	<1%----------0%

Whether you agree with this scheme or not, it brings up two main questions

1. **Are these national, district, area, or village percentages?**
1. **What is the sensitivity of the tool you are using to determine prevalence?**

My history of the Kato-Katz thick smear stool assay

- **Katz, Chaves & Pelligrino (1972) Rev. Inst. Med. Trop. Sao Paulo 14:397**
  - **Revolutionized the process of getting intensity and prevalence data from large numbers of people, i.e., made stool exams more feasible on a population level**
  - **Worked very well at the start of a control program in areas of high intensity and corresponding high prevalence**
  - **Used extensively and established as part of WHO guidelines for morbidity control programs**
  - **Used extensively by research programs – most often testing 3 consecutive stools, 2 Kato-Katz slides on each stool**
  - **Documented day-to-day, and intra-stool variability, especially in sites with moderate to low intensity and corresponding prevalence – day-to-day variation is simply biologic, while intra-stool variation is a sampling error based on the amount of stool evaluated**

◆ Acknowledged low sensitivity, high specificity of the Kato-Katz

- **Based on multiple publications by multiple different investigators, it was widely stated and widely acknowledged that in situations with high mean intensities of infection (and of corresponding high prevalence) the Kato-Katz assay provided close to true prevalence estimates for morbidity control programs and worked well for this purpose**

- **However, even then the dependence on a single stool examination led to underestimates of true prevalence, and in places of lower intensities of infection (~ 100 epg by Kato-Katz) the ability of the assay to provide true prevalence estimates became less and less as intensities decreased**

- **Most of those in this field will remember a series of summary and statistical publications that pulled this together – over 20 years ago**

  - **de Vlas, Gryseels, et al., (1992) Parasitology, 104:451**
  - **de Vlas, Gryseels, et al., (1993) Parasitology Today, 9:305**
  - **de Vlas, Engels, et al., (1997) Parasitology, 114:113**

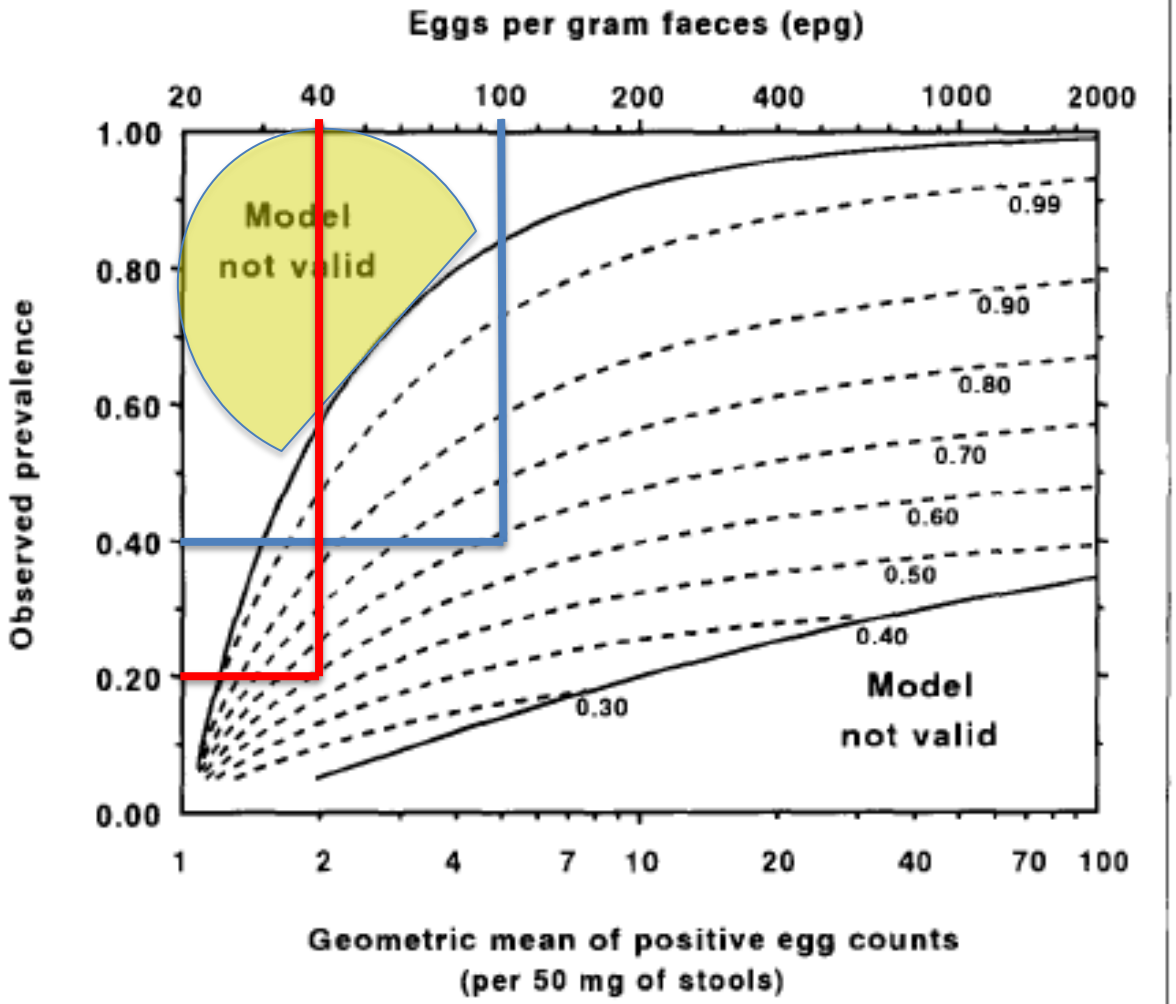


Fig. 1. Pocket chart to estimate true Schistosoma mansoni prevalences. For each combination of observed prevalence and geometric mean of positive egg counts, the estimated proportion of individuals that harbour at least one worm pair can be read from the broken contour lines. The model on which the predictions are based applies to pre-control situations, and holds only between the solid lines. The chart is based on egg counts obtained in 50 mg stools, and should preferably be applied for separate age groups (eg. five-year age classes in children, and 10–20-year age classes in adults).

"The upper left corner combines very high prevalences with very low mean egg counts, which would not satisfy the generally accepted negative binomial distribution for worm loads."

"However, such observations could result from control measures in which only" *(or mainly)* "heavily infected persons are treated" *(or effectively treated)*

de Vlas, Gryseels, et al., (1993; Parasitology Today)

What do you want in a tool that will help you:

- Map to start a “Gaining” control program
- Monitor the impact of a “Gaining” or “Sustaining” control program
- Determine if it is time to switch strategies
- Specifically in the Americas, to determine if it is time to initiate an “Elimination” program

What is the Target Product Profile (TPP) for each of these – how do they differ?

What do you want in a tool that will help you:

- **Map to start a "Gaining" control program**
  - Low sensitivity is okay, High specificity is good
- **Monitor the impact of a "Gaining" or "Sustaining" control program**
  - Need more sensitivity, High specificity is good
- **Determine if it is time to switch strategies**
  - Need even more sensitivity, High specificity is good
- **Specifically in the Americas, to determine if it is time to initiate an "Elimination" program**
  - Must have high sensitivity, High specificity is good
- **Post-elimination requires excellent sensitivity & excellent specificity based on exposure or infection**

Is there a better mapping tool for *S. mansoni* & can it be used for decision making as we move forward?

The first question is:

"Is the POC-CCA urine assay just as good as a Kato-Katz for mapping *S. mansoni* prevalence?"

Based on 4305 children in 5 countries in 63 schools with widely varying prevalence levels……

Is it "just as good as a Kato/Katz" for mapping purposes?

YES!

(& it is on urine, on-site, and MORE sensitive at low epg)

Colley DG, Binder S, Campbell C, King C, Tchuem Tchuente, L-A, N'Goran E, Erko B, Karanja DMS, Kabatereine N, van Lieshout, L, Rathbun S.
A five-country evaluation of a point-of-care cathodic antigen urine assay for the prevalence of *Schistosoma mansoni*
Am. J. Trop. Med. Hyg., 88:426-432, 2013

But there is no gold standard for diagnosis – so the discussion goes on, and you do the best you can…the POC-CCA is now being tried in many countries on a large scale (some by SCORE with National Programs)

Even as it is being used the POC-CCA assay should continually be studied to determine its potential flaws and ease of implementation

More POC-CCA Evaluations

Pauline Mwinzi, Nupur Kittur, Elizabeth Ochola, Phillip Cooper, Daniel G. Colley and Charles H. King

4 different evaluations of POC-CCA were done in 2013-2014 in Kisumu, Kenya

1. Cassette batch variation – "no real variation"
2. Intra-reader reliability – "2% variation, insignificant"
3. Day to day variability in CCA and KK
4. CCA evaluation after PZQ treatment

Many other groups are also doing and publishing various evaluations of the POC-CCA vs. Kato-Katz; These next slide are our most recent data evaluating #3 and #4 above

3. Day-to-day variability of CCA and KK

METHOD: 73 participants; Each had CCA tests on 5 consecutive days' urines; and K-K tests on 3 consecutive days' stools (2 slides each); Subjects representative of a moderate-to-high prevalence area (44% on the first K-K stool/2 slides)

What is the schistosomiasis prevalence based on one or several POC-CCA & Kato-Katz tests sampling 73 Kenyan school children?

CCA		Prevalence (73 participants) N (%)
Day	1	59 (81%)
	2	62 (85%)
	3	62 (85%)
	4	62 (85%)
	5	64 (88%)
At least 1 of 5 CCA tests positive		69 (94%)

K-K		Prevalence (73 participants) N (%)
Day	1	32 (44%)
	2	31 (43%)
	3	30 (41%)
At least 1 of 3 K-K tests positive		51 (70%)

How many participants have a consistent result for 3 CCA tests?

Result of 3 CCA tests for 73 participants	Number of participants (%)
All 3 negative (0)	5 (7%)
All 3 positive (trace/1/2/3)	55 (75%)
Mixed positive and negative results	13 (18%)

} 82%

How many participants have a consistent result for 3 KK tests?

Result of 3 KK tests (2 slides taken together)	Number of participants (%)
All 3 negative (0)	21 (29%)
All 3 positive	15 (20%)
Mixed positive and negative results	35 (48%)

} 49%

This slide says both assays vary some, but the K-K varies a lot more than the POC-CCA

So, if you are only assaying once – like National Programs (even in the "44%" prevalence range) ……., use the POC-CCA

Sensitivity & Specificity analysis of POC-CCA one day testing evaluated against a "gold standard" of at least 1 of 8 tests (5 CCA and 3 KK) being positive

"Gold standard" At least 1 of 8 tests +ve (5 CCA + 3 KK)	Sensitivity % (95% CI)	Specificity % (95% CI)
CCA day 1	85.5 (74.9- 92.8)	100 (40.2- 100)
CCA day 2	89.9 (80.2- 95.8)	100 (40.2- 100)
CCA day 3	89.9 (80.2- 95.8)	100 (40.2- 100)
CCA day 4	89.9 (80.2- 95.8)	100 (40.2- 100)
CCA day 5	92.7 (83.9- 97.6)	100 (40.2- 100)

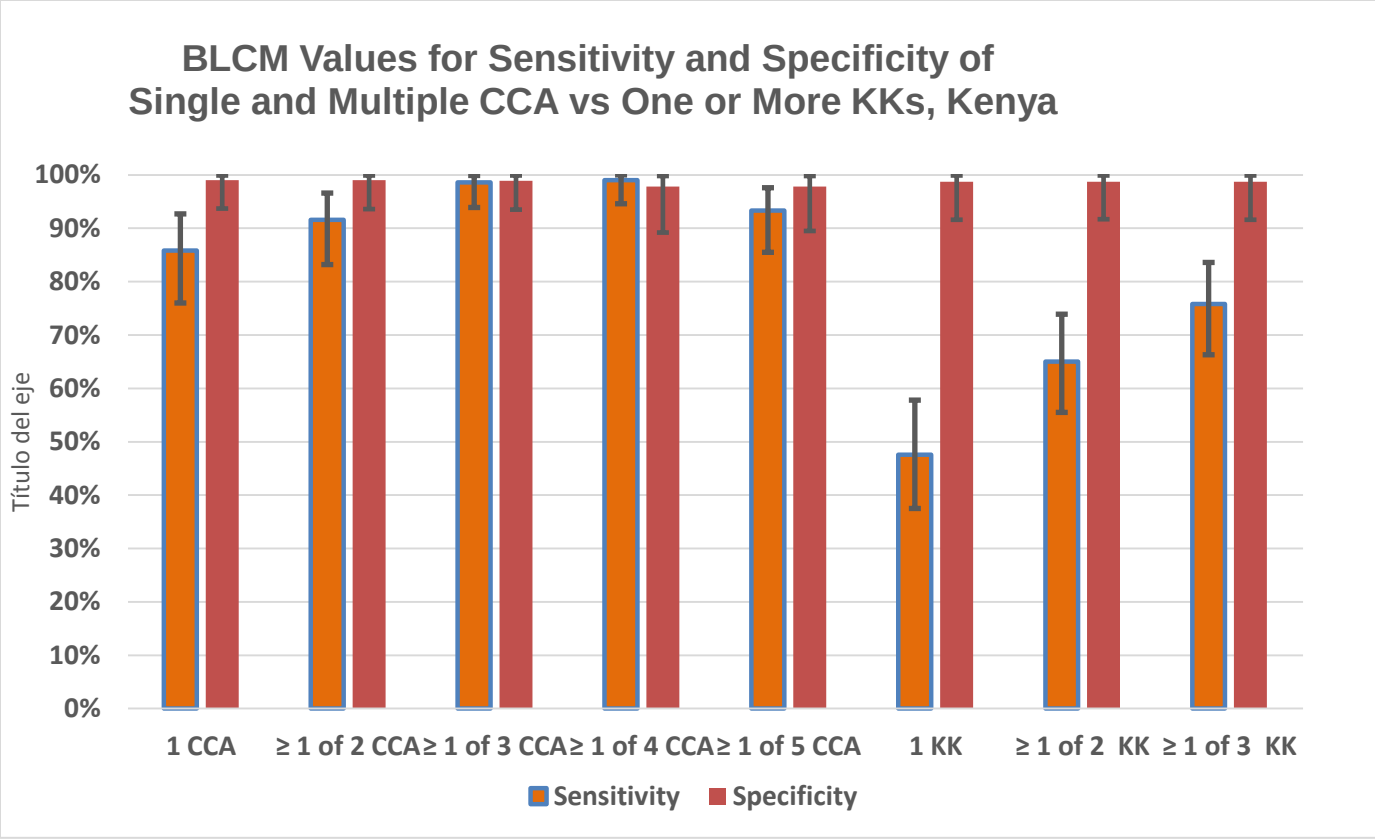
About Specificity:

How does the POC-CCA assay do in areas that have never been endemic for schistosomiasis – but are endemic for STH?

	# Tested	# Positive	% False +
Ethiopia	100	1	1%
Ecuador	74	0	0%

Charlie King took the same data & did Bayesian Latent Class Modeling

Test	Sensitivity	Sn lower CI	Sn upper CI	Specificity	Sp lower CI	Sp upper CI
1 CCA	0.858	0.76	0.927	0.99	0.937	0.999
≥ 1 of 2 CCA	0.916	0.832	0.966	0.99	0.936	0.999
≥ 1 of 3 CCA	0.986	0.939	0.999	0.989	0.935	0.999
≥ 1 of 4 CCA	0.99	0.946	1	0.978	0.892	0.998
≥ 1 of 5 CCA	0.933	0.855	0.976	0.978	0.895	0.998
1 KK	0.476	0.375	0.578	0.987	0.916	0.999
≥ 1 of 2 KK	0.65	0.555	0.739	0.987	0.917	0.999
≥ 1 of 3 KK	0.758	0.663	0.836	0.987	0.916	0.999



This BLCM was developed using data from all 73 subjects, assessing the most likely performance characteristics of 1 up to 5 daily POC-CCA results, and 1 up to 3 daily K-K stool results, guided by earlier POC-CCA specificity data from 100 Ethiopian and 74 Ecuadorian children from non-endemic (*S. mansoni*) areas

The data from both analyses are pretty much the same for the POC-CCA

Is there a correlation between having a moderate/high egg count by KK and a positive POC-CCA test score?

(i.e., Can you get semi-quantitative intensity data from the POC-CCA assay?)

"YES"

For the 10 participants with moderate infections by KK (104- 452 epg)

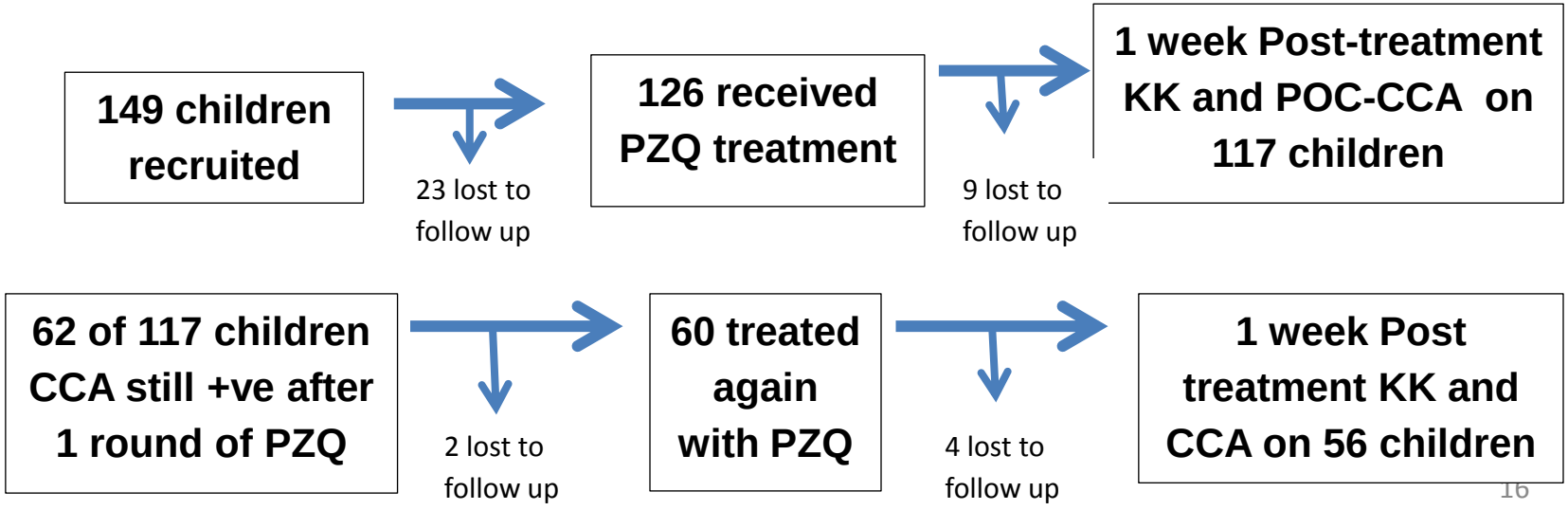
- **The CCA results were all positive: (Intensity 1, 2 or 3) (No Trace);**
  - **i.e, all subjects with moderate or high egg count have an unambiguously positive POC-CCA result**
- **Their POC-CCA scores correlate well by Spearman's with their egg counts**

Correlation of Mean epg with	Spearman's rho	P value
Day 1 CCA	0.630	<0.001
Day 2 CCA	0.675	<0.001
Day 3 CCA	0.652	<0.001
Day 4 CCA	0.696	<0.001
Day 5 CCA	0.601	<0.001

- **4. CCA evaluation after PZQ treatment**

- **METHOD: Selected 149 school children in an area of 10-15% prevalence**
- **Kato-Katz (-) (3X2 = 6 slides) & POC-CCA (+) (1 urine)**
- **Treat all (PZQ); 7 days later K-K,1 stool/2 slides; POC-CCA, 1 urine**
- **Children still (+) by POC-CCA; Treat again (PZQ)**
- **7 days later K-K, 1 stool/2 slides; POC-CCA, 1 urine**
- **Children still (+) by POC-CCA; Treat again (PZQ)**

Post-PZQ study design



Plus/Minus POC-CCA Results Following the First and Second Treatments

1st Treatment results by POC-CCA — **56 of 117 turned CCA-negative (i.e., 48% were "cured" based on CCA)**

2nd Treatment results by POC-CCA — **19 of 60 turned CCA-negative (i.e., 34% were cured" based on CCA)**

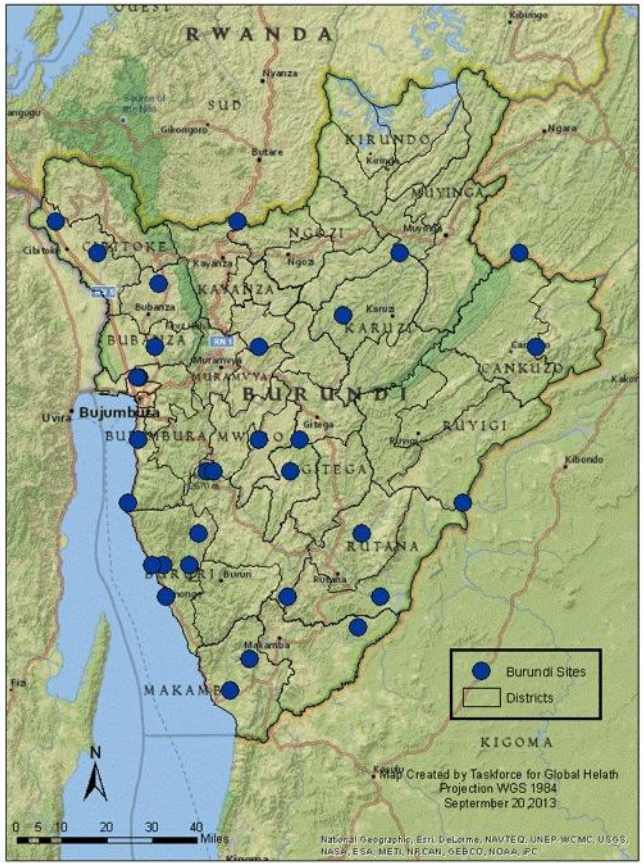
Literature usually states that PZQ has 70%-90% cure rates – but that is always assaying cure by Kato-Katz – which is known to be insensitive at low intensities of infection……..

I think that when you use a more sensitive assay, many of the K-K (-)/POC-CCA (+) are real, i.e., they still have some worms, they are not cured – therefore standard cure rates are high estimates based on a test of low sensitivity

On to some country-wide mapping done in Burundi by the MOH, SCI & SCORE

At an NTD meeting in Paris in April 2014, Dr. Onesime Ndayishimiye (NTD Director, Burundi) speaks…….and Bill Gates, Margaret Chan and Chris Viehbacher are listening !

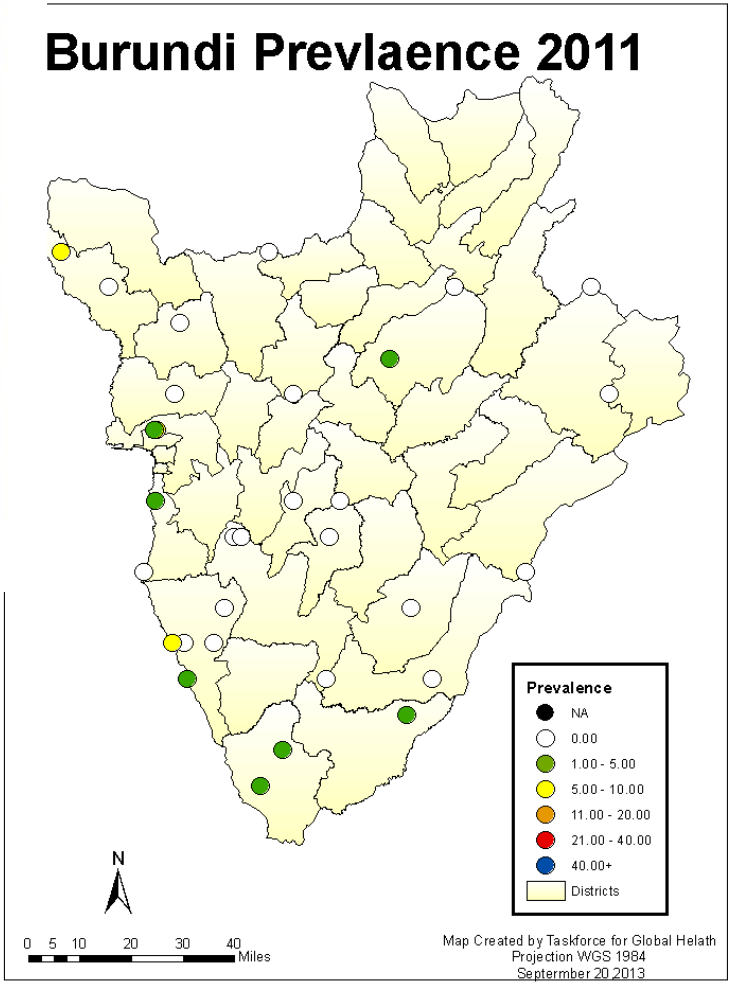
Burundi Sites

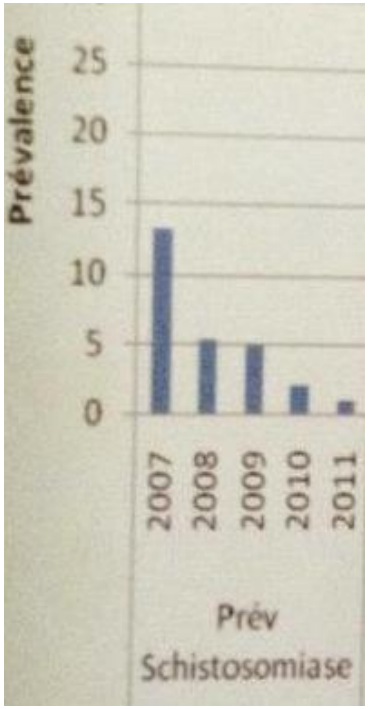


Burundi has 31 sentinel sites where they have been monitoring prevalence for 6 years while doing annual MDA with PZQ

This is very good, but <u>more complete mapping is also needed to move ahead</u>

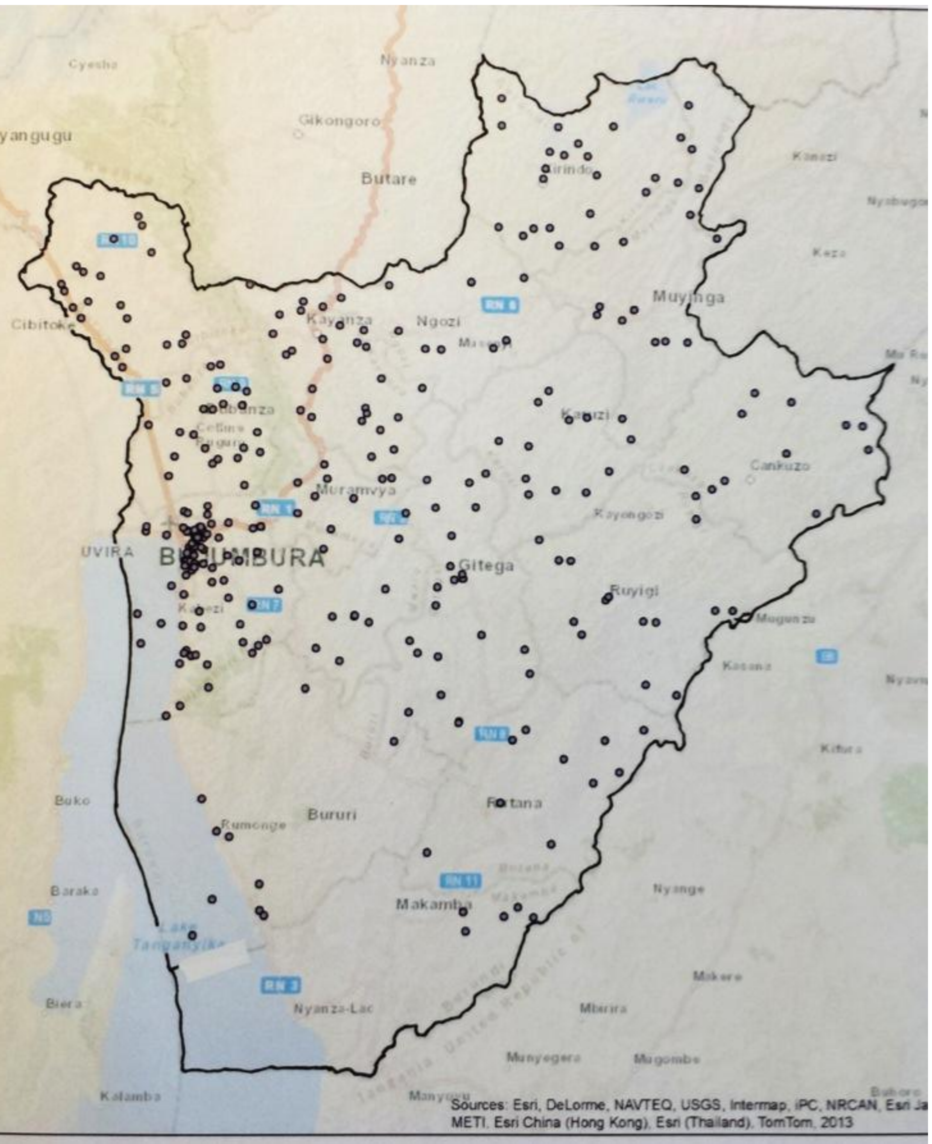
Burundi Prevlaence 2011

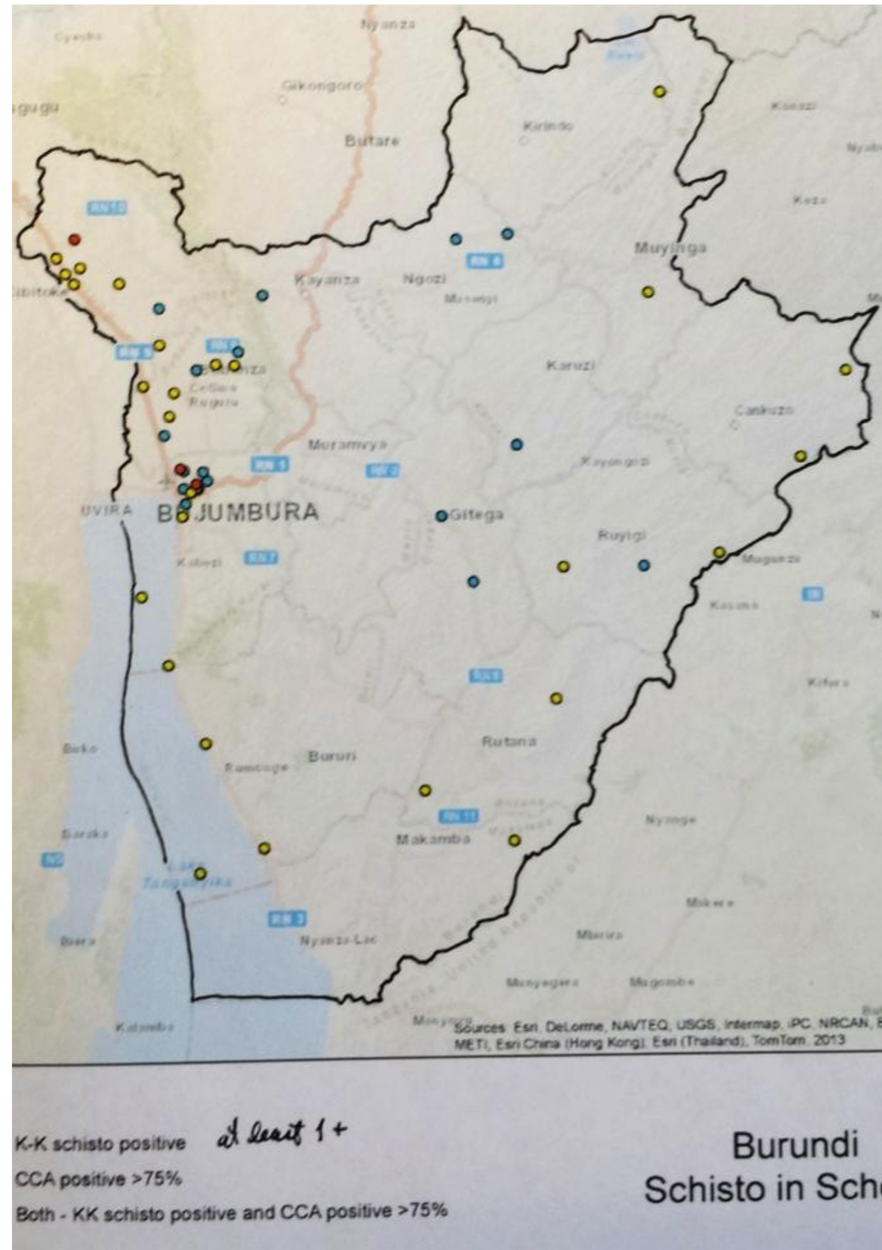




MOH-NTD/SCI/SCORE Program just finished mapping 50 9-12 y/o children in each of > 400 school across Burundi (and Rwanda)

All by 1 POC-CCA and over half of those also by Kato-Katz (1 stool/2 slides)





….and the country-wide prevalence of *S. mansoni* (based on 20,315 children done by POC-CCA & 11,523 children also done by Kato-Katz):

- **By Kato-Katz (1 stool/2 slides) = 1.5%**
- **By POC-CCA (1 urine) = 42%**

70% of the POC-CCA positives were “Trace”
18% of the POC-CCA positives were “1”
6% of the POC-CCA positives were “2”
6% of the POC-CCA positives were “3”

I think we need to start a major discussion of how to eliminate schistosomiasis when there are a lot more low intensity infections out there than we think based on Kato-Katz
(even though we always really knew that was true)

And in the next section on morbidity control we can discuss the evidence that subtle morbidity is real *and a product of even low intensity egg production and inflammatory responses to them*

Based on the POC-CCA assay data that I have shown you, and on what many other groups have published on the POC-CCA assay

I propose that the POC-CCA is not a perfect test, but it is a better test to than a Kato-Katz for S. mansoni surveys when the Kato-Katz prevalence is </= 5%

The data say that most (if not all) Kato-Katz (-)/ POC-CCA (+) test on someone in a "formerly endemic" area is likely to be a "probable low level infection" and worthy of follow-up to get to elimination

Back to TPPs of assays for different situations (in my opinion)

What do you want in a tool that allows you to approach the switch from "Sustaining" control to elimination?

Good sensitivity below 60-80 epg by multiple Kato-Katz stools

Reasonable specificity; Ease of use and specimen collection

POC-CCA

What do you want in a tool that allows you to decide whether to move to an elimination strategy?

High sensitivity below 20-50 epg by multiple Kato-Katz stools

Reasonable specificity; Ease of use and specimen collection

POC-CCA – perhaps with more training or a reader

What do you want in a tool that allows you to achieve elimination?

Very high sensitivity; High specificity

Ease of specimen collection & High throughput, could be in lab

UCP-CAA; possibly Urine Nucleic Acid assays

What do you want in a tool that allows you to develop a realistic surveillance protocol for use after you have achieved elimination?

Very high sensitivity; Very high specificity

Ease of specimen collection; Possible pooling; High throughput

Ab assays, to be developed; mulitiplexing

Thanks for listening to some of the public health challenges (opportunities) that schistosomiasis presents

SCORE
RESEARCH for CONTROL and ELIMINATION

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Global Health Through Research