Morbidity Operational Research for Bilharziasis Implementation Decisions (MORBID) Project

Defining morbidity control to set targets and inform programmatic decision-making

The findings and conclusions in this presentation are those of the author and do not necessarily represent the views of the Centers for Disease Control and Prevention.



## Maximizing Control Strategy

- Preventive chemotherapy targets and thresholds for schistosomiasis based on small studies conducted during 1970's & 80's, combining with STH
- At that time, had limited PZQ so guidelines focused on life threatening morbidity
- Now have broader understanding of morbidity & available drug donations
- SCORE & SCI data show many villages below thresholds at baseline or achieve control or EPHP after 1-2 rounds of MDA, yet morbidity is still present

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#### MORBIDITY IN SCHISTOSOMIASIS MANSONI IN RELATION TO INTENSITY OF INFECTION: STUDY OF A COMMUNITY IN MACHAKOS, KENYA\*

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Abstract. An approximation of the entire population (83%) of the village of Lower Nduu, Machakos Kenya, was examined in a cross-sectional study of the prevalence and intensity of schistosomiasis mansoni correlated with morbidity as determined by standard medical examination. The 416 individuals in 90 households studied had a male female ratio of 44:56 and an age structure in which more than 50% were below age 20. Malaria was of very low endemicity in the area as were intestinal helminths and Schistosoma haematobium. S. mansoni infection as determined by quantitative Kato thick smears had an overall prevalence of 82% with a peak of 98% in the 10 to 19 age group and a decline to about 70% in the older population. With respect to intensity, 12% were uninfected, 28% had light (10-100 eggs/g), 21% moderate (101-400), and 33% heavy (>401) infections; 16% had egg counts over 1,000/g. Peak intensity occurred in females at ages 10 to 14 years (1,026 eggs/g) and in males at age 20 to 24 years (1,019 eggs/g). A history of weakness or inability to work occurred in only a small proportion of the population and was not correlated with intensity of infection. Abdominal pain was significantly more prevalent in the most heavily infected individuals (>1.000 eggs/g). Hepatomegaly occurred more frequently in those more heavily infected (>400 eggs/ g) and splenomegaly, which was not observed in the uninfected population, occurred in 7% of those with egg counts greater than 400/g. Twelve individuals, or almost 3% of the population studied, had hepatosplenomegaly: most of them were under 21 years of age, all of them were infected with S. mansoni, and 58% had high egg counts. Liver function tests were mostly within normal limits. Two of the patients had esophageal varices on barium swallow, but these and 7 others studied by splenoportography had patent portal veins.

Schistosomiasis is generally acknowledged to be the major chronic helminth infection of mankind.<sup>1</sup> While the clinical manifestations of schistosomiasis mansoni have been well studied in individual cases or hospital populations, there is need for investigations of the significance of the infection in communities in endemic areas. Recently, we have developed a cross-sectional method with which the prevalence and intensity of *Schistosoma mansoni* infections as determined by quantitative egg counts are correlated with morbidity as determined by standard medical examination<sup>2.3</sup> This method was first applied in a study of school-

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children with different levels of infection on the island of St. Lucia,<sup>2</sup> where prevalence and intensity of schistosomiasis is relatively low. The methodology was refined in a study of a group of adult male Yemeni farm workers in the U.S.A.,<sup>3</sup> who provided a unique opportunity to study the longevity of the worms in an infected population outside of an endemic area.

In the present investigation plans were made to examine an entire community in an area endemic for schistosomiasis. Lower Nduu, a village of approximately 500 people in the Machakos district of Kenya, was selected on the basis of preliminary studies which revealed a high prevalence rate of *Schistosoma mansoni* infection in children below 16 years of age.<sup>4</sup> In addition, the demography of the area had been completely determined and is being followed by the Dutch Medical

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#### *S. haematobium*: < 5% High Intensity Infections



#### *S. haematobium*: < 1% High Intensity Infections



#### *S. mansoni*: < 5% High Intensity Infections



#### *S. mansoni*: < 1% High Intensity Infections



## **Operational Research Questions**

How can we improve on the current morbidity control strategy:

- 1. What is the optimal morbidity <u>marker</u> for *S. mansoni* and *S. haematobium*?
- 2. What is the optimal morbidity <u>goal</u> for each species?

## Draft protocol to define morbidity control targets

- By better defining morbidity control, programs will have better targets to measure progress
- Targets useful to design control programs and track progress
- Targets also necessary to identify problematic areas (e.g., "hotspots")
- Goal is to employ standardized protocols to identify morbidity markers or infection level correlates of morbidity that can be measured easily by control programs to guide program decision making
- Different morbidity markers may have different relationships with prevalence or intensity of infection



#### Assumptions and Hypotheses

- Because some schistosomiasis morbidities are not specific, villages with 0% prevalence included to establish "background" morbidity
- Also include groups with 0-10%, 10-25%, and > 25% prevalence
- Within each prevalence group, include PSAC, SAC, and adult age categories as different age groups display different morbidities
- *S. mansoni* and *S. haematobium* likely to have different infection level correlates with morbidity and therefore different targets for morbidity control

## S. mansoni protocol

Age group	Infection measures	Morbidity measures	# per village	# villages
2-6 years (PSAC)	<ul> <li>KK 1 stool 4 slides</li> <li>Count Sm, STH+/-</li> <li>POC-CCA 1 urine, freeze aliquot for UCP-CAA</li> </ul>	<ul> <li>FOB</li> <li>Calprotectin</li> <li>Anthropometry</li> <li>US (liver, spleen, PBT, PV)</li> <li>Fingerstick for Hb, Ab, malaria</li> </ul>	50-75	30 (0% KK+ in 9-12 y.o.) 30 (0.1-10% KK+ in 9-12 y.o.) 30 (10-25% KK+ in 9-12 y.o.) 30 (> 25% KK+ in 9-12 y.o.)
7-15 years (SAC and adolescents)	<ul> <li>KK 1 stool 4 slides</li> <li>Count Sm, STH+/-</li> <li>POC-CCA 1 urine, freeze aliquot for UCP-CAA</li> </ul>	<ul> <li>FOB</li> <li>Calprotectin</li> <li>Anthropometry</li> <li>US (liver, spleen, PBT, PV)</li> <li>Fingerstick for Hb, Ab, malaria</li> <li>Venous blood in subset for morbidity biomarkers</li> </ul>	50-75	30 (0% KK+ in 9-12 y.o.) 30 (0.1-10% KK+ in 9-12 y.o.) 30 (10-25% KK+ in 9-12 y.o.) 30 (> 25% KK+ in 9-12 y.o.)
20-50 years (Adults)	<ul> <li>KK 1 stool 4 slides</li> <li>Count Sm, STH+/-</li> <li>POC-CCA 1 urine, freeze aliquot for UCP-CAA</li> </ul>	<ul> <li>FOB</li> <li>Calprotectin</li> <li>US (liver, spleen, PBT, PV)</li> <li>Fingerstick for Hb, Ab, malaria</li> <li>Venous blood in subset for morbidity biomarkers</li> </ul>	50-75	30 (0% KK+ in 9-12 y.o.) 30 (0.1-10% KK+ in 9-12 y.o.) 30 (10-25% KK+ in 9-12 y.o.) 30 (> 25% KK+ in 9-12 y.o.)

# S. haematobium protocol

Age group	Infection measures	Morbidity measures	# per village	# villages
2-6 years (PSAC)	<ul> <li>UF 1 urine, 2X 10ml filtrations— freeze aliquot for UCP-CAA</li> <li>Count Sh eggs</li> </ul>	<ul> <li>Haemastix/gross hematuria/proteinuria</li> <li>US (bladder)</li> <li>Anthropometry</li> <li>Fingerstick for Hb, Ab, malaria</li> </ul>	50-75	30 (0% UF+ in 9-12 y.o) 30 (0.1-10% UF+ in 9-12 y.o.) 30 (10-25% UF+ in 9-12 y.o.) 30 (> 25% UF+ in 9-12 y.o.)
7-15 years (SAC and adolescents)	<ul> <li>UF 1 urine, 2X 10ml filtrations— freeze aliquot for UCP-CAA</li> <li>Count Sh eggs</li> </ul>	<ul> <li>Haemastix/gross hematuria/proteinuria</li> <li>Anthropometry</li> <li>US (bladder, ureters)</li> <li>Genital schistosomiasis questionnaires</li> <li>Fingerstick for Hb, Ab, malaria</li> <li>Venous blood in subset for morbidity markers</li> </ul>	50-75	30 (0% UF+ in 9-12 y.o) 30 (0.1-10% UF+ in 9-12 y.o.) 30 (10-25% UF+ in 9-12 y.o.) 30 (> 25% UF+ in 9-12 y.o.)
20-50 years (Adults)	<ul> <li>UF 1 urine, 2X 10ml filtrations— freeze aliquot for UCP-CAA</li> <li>Count Sh eggs</li> </ul>	<ul> <li>Haemastix/gross hematuria/proteinuria</li> <li>US (bladder, ureters)</li> <li>Genital schistosomiasis questionnaires (incl. subfertility)</li> <li>Fingerstick for Hb, Ab, malaria</li> <li>Venous blood in subset for morbidity markers</li> </ul>	50-75	30 (0% UF+ in 9-12 y.o) 30 (0.1-10% UF+ in 9-12 y.o.) 30 (10-25% UF+ in 9-12 y.o.) 30 (> 25% UF+ in 9-12 y.o.)

#### Other considerations

- Sites of primary interest are those that have undergone 3 rounds of MDA
  - Most similar to country programs
  - Treatment may promote reduced morbidity in subsequent (re)infection
- However, inclusion of sites that have not had MDA also informative
- Adults less likely to reflect benefits of MDA in these studies (but maybe, re: SCORE)
- Proposed to conduct in 4 (3 +1) study sites per species = 8 study sites (144,000 to 216,000 overall participants)

## Pilot Study

- Some funds available to conduct pilot study to evaluate feasibility of the variety of proposed tests and confirm their utility as morbidity markers (e.g., calprotectin)
- 2 countries: 1 for *S. mansoni* (Kenya) and 1 for *S. haematobium* (Malawi) based on previous experience with local investigators and high likelihood of success
- Only including highest (> 25% prevalence) and lowest (0% prevalence) groups to maximize likelihood of observing differences

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#### S. mansoni assessment measures

- 1. Demographic data: age, sex, village of residence, length of residence, individual's recollection of previous treatment with praziquantel, village history previous number of rounds of MDA, village prevalence prior to first MDA
- 2. Stool exam (all ages): one stool sample will be obtained from each individual. Four Kato-Katz slides will be prepared from each stool sample. Schistosome eggs will be enumerated to calculate stool eggs per gram. Eggs from soil transmitted helminths will be noted as positive or negative.
- 3. Fecal Occult Blood (all ages): the Beckman Coulter Hemoccult II SENSA chromatographic test or its equivalent will be used to detect fecal occult blood in stool samples.
- 4. Calprotectin (all ages): calprotectin is a marker of intestinal inflammation that can be detected in stool samples. A point of care chromatographic immunoassay (Quantum Blue or its equivalent) will be used.
- 5. POC-CCA (all ages): a urine sample will be obtained from each individual and tested by POC-CCA. Tests will be scored at trace, 1+, 2+, or 3+ based on the intensity of the test band in relation to the control band. Store an aliquot at -20C for UCP-CAA testing.
- 6. Anthropometry (PSAC and SAC): height, weight, and mid upper arm circumference will be measured using standard procedures. Z scores will be calculated to determine prevalence of stunting or wasting.
- 7. Ultrasound (SAC and adults): the Niamey protocol will be used to determine liver image pattern, hepatomegaly, splenomegaly, portal branch thickening, and portal vein diameter.
- Venous blood samples could be obtained to assess malaria and anemia as well as investigate potential markers of fibrosis (e.g., osteopontin, periostin) or bacterial translocation (e.g., LPS, SCD14m, intestinal Fatty Acid Binding Protein, α-2 macroglobulin, C-reactive protein, hepcidin)

#### S. haematobium assessment measures

- 1. Demographic data: age, sex, village of residence, length of residence, individual's recollection of previous treatment with praziquantel, village history previous number of rounds of MDA, village prevalence prior to first MDA
- 2. Urine exam (all ages): one urine sample will be obtained from each individual. Two aliquots of 10 ml of urine will be filtered. Filters will be mounted on slides and stained with iodine to facilitate schistosome egg enumeration.
- 3. Each urine specimen will be assessed for gross hematuria. Dipsticks will be used to detect microhematuria and proteinuria.
- 4. An aliquot of urine will be stored at -20C for subsequent UCP-CAA testing.
- 5. Anthropometry (PSAC and SAC): height, weight, and mid upper arm circumference will be measured using standard procedures. Z scores will be calculated to determine prevalence of stunting or wasting.
- 6. Ultrasound: ultrasound will be used to measure shape of the bladder, evidence of inflammation or bladder fibrosis in all ages. Diameters of ureters will be measured in SACs and adults.
- 7. Genital schistosomiasis questionnaire (SAC and adults): a questionnaire will be used to assess sex-specific symptoms consistent with genital schistosomiasis; subfertility questions included for adult females
- 8. Venous blood samples could be obtained to assess malaria and anemia as well as investigate potential markers of fibrosis (e.g., osteopontin, periostin).

#### Assumptions and Hypotheses

- Sample size calculated assuming a threshold effect curve of 10% (assumption per current WHO guidelines)
- Villages with 0% prevalence included to establish background morbidity
- Also include groups with 0-10%, 10-25%, and > 25% prevalence
- Monte Carlo simulations (Ryan Wiegand) used to determine number of villages needed per prevalence group to provide 80% power with different breakpoints: 30 villages per prevalence group with 50-75 people per group able to detect a breakpoint of 7.5% with a background morbidity of 10%
- *S. mansoni* and *S. haematobium* likely to have different infection level correlates with morbidity and therefore different targets for morbidity control
- Treatment may promote reduced morbidity in subsequent (re)infection
- Within each prevalence group, include PSAC, SAC, and adult age categories as different age groups display different morbidities



Simulations done assuming 10% background morbidity. N per group is the number of villages within infection ranges (0%, 0.1 to 10%, 10% to 25%, > 25%). To detect a breakpoint of 7.5%, need <u>30 villages per group</u> to have 80% power if the SD is as high as 4 (larger variability among villages).

N per group



Probability

Bottom line: need groups of 50 to 75 per age category