Title: Importance and effectiveness of improving treatment beyond school-aged children in high endemicity *Schistosoma mansoni* communities

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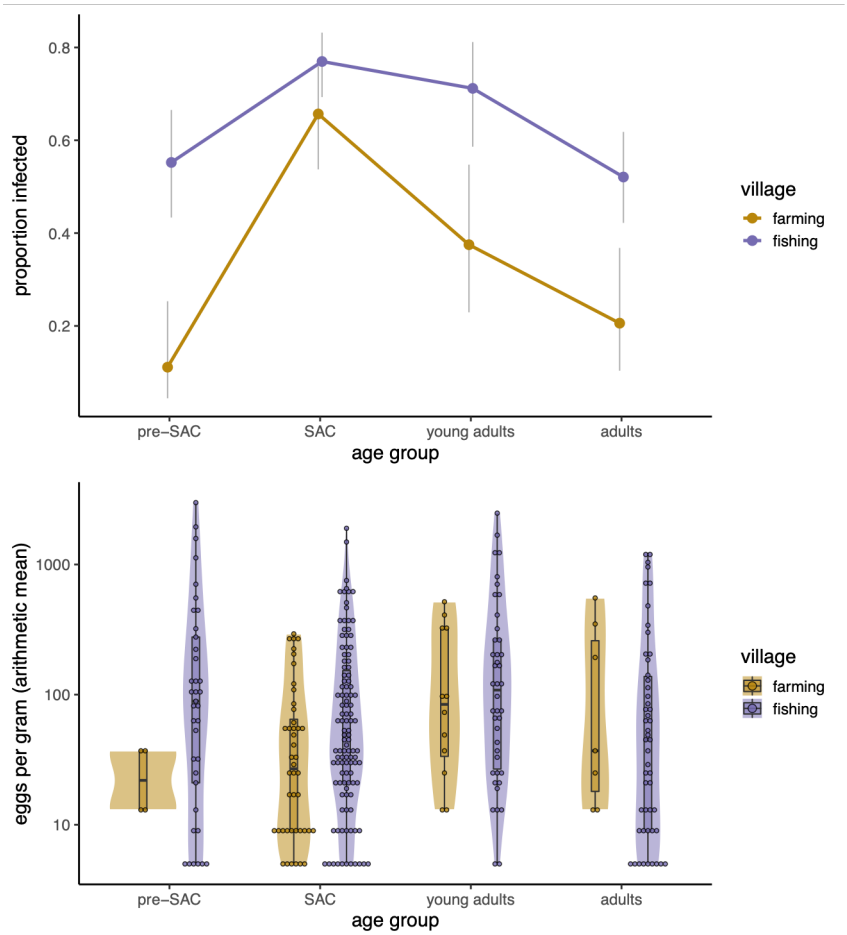
ABSTRACT
Background. Hotspots of schistosomiasis persist in Uganda and other sub-Saharan African countries despite nearly two decades of preventive chemotherapy through mass drug administration (MDA). Although praziquantel is donated for free and recommended for community-wide treatment in high endemic areas, coverage remains low and global supplies are limited. A key question is how to optimize drug distribution to maximise success, reduce transmission and minimize heavy infection intensities.

Methods. We conducted a longitudinal survey of 640 individuals aged nine months to 80 years old residing in Bugoto, Mayuge District, Uganda, a high endemic *Schistosoma mansoni* community. Stool samples were collected for Kato-Katz and isolation of miracidia for population genetic analyses. Reinfection and parasite genetic diversity was re-evaluated at five and 18 months after treatment and compared between age groups, alongside travel survey data.

Findings. Following national MDA, infection intensities were higher in preschool-aged children (PSAC) and young adults compared to SAC. High infection intensities were associated with water contact frequency and duration, ineligibility for MDA, and young adults systematically not offered treatment. Following observed treatment, SAC had the highest reinfection rates. Examination of parasite genetic structure revealed significant differentiation between age groups but not across timepoints. While SAC are often the focus of control programs, we provide epidemiological and genetic evidence that these target groups can be rapidly re-infected by an untreated reservoir of high-risk PSAC and mobile adults importing parasites.

Interpretation. Improving praziquantel treatment coverage in age groups beyond SAC will help high endemic regions reach targets for elimination of schistosomiasis as a public-health burden.

Figure 1. Proportion and intensity of *S. mansoni* by age group and village (n = 544). A) Proportion of infected individuals in each age group by village. 95% confidence intervals are in grey and calculated with Agresti-Coull methods. All age groups, except for SAC, have significantly lower proportion of individuals infected in the farming village. B) Violin plots shown the distribution of intensity of infections by age group and village. Twice as many individuals were sampled in the fishing village, reflecting the relative populations. Note the y-axis in figure B is on a log scale. Both measured by three days of duplicate Kato-Katz thick smears.



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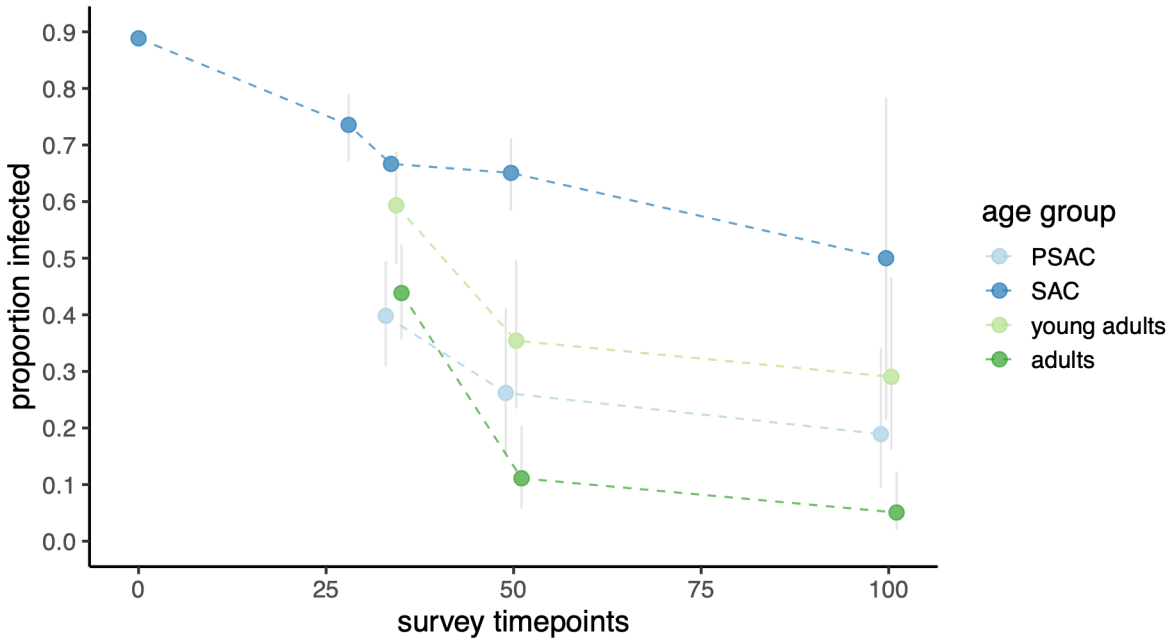

Figure 2. Reinfection following treatment in the different age groups. The proportion of infected individuals in each age group (PSAC=preschool-aged children, SAC= enrolled and non-enrolled school-aged children, young adults=15 to 29 years old and adults= >29 years old) is shown at each major sampling point. 95%CI are shown for each point and are calculated with the Agresti-Coull method. Only 4 non-enrolled SAC were sampled at the last timepoint (100 weeks), hence the very large confidence intervals.

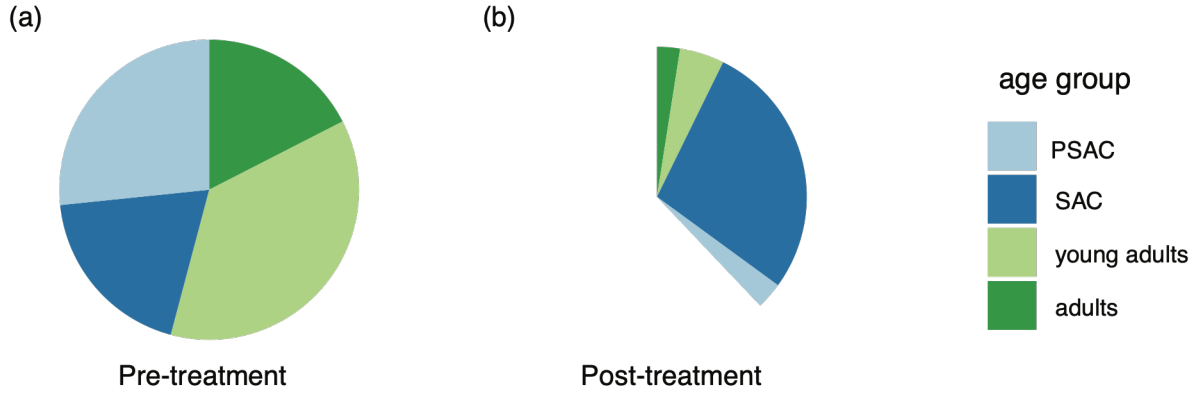

Figure 3. Estimated contribution of age groups to intestinal schistosomiasis transmission. A) At pre- treatment sampling timepoint the arithmetic mean and relative population proportion was used to estimate the contribution of each age class to transmission in the community. B) Following treatment, the mean infection intensities of PSAC, young adults and adults dropped substantially, whereas SAC were reinfected to a similar infection intensity.

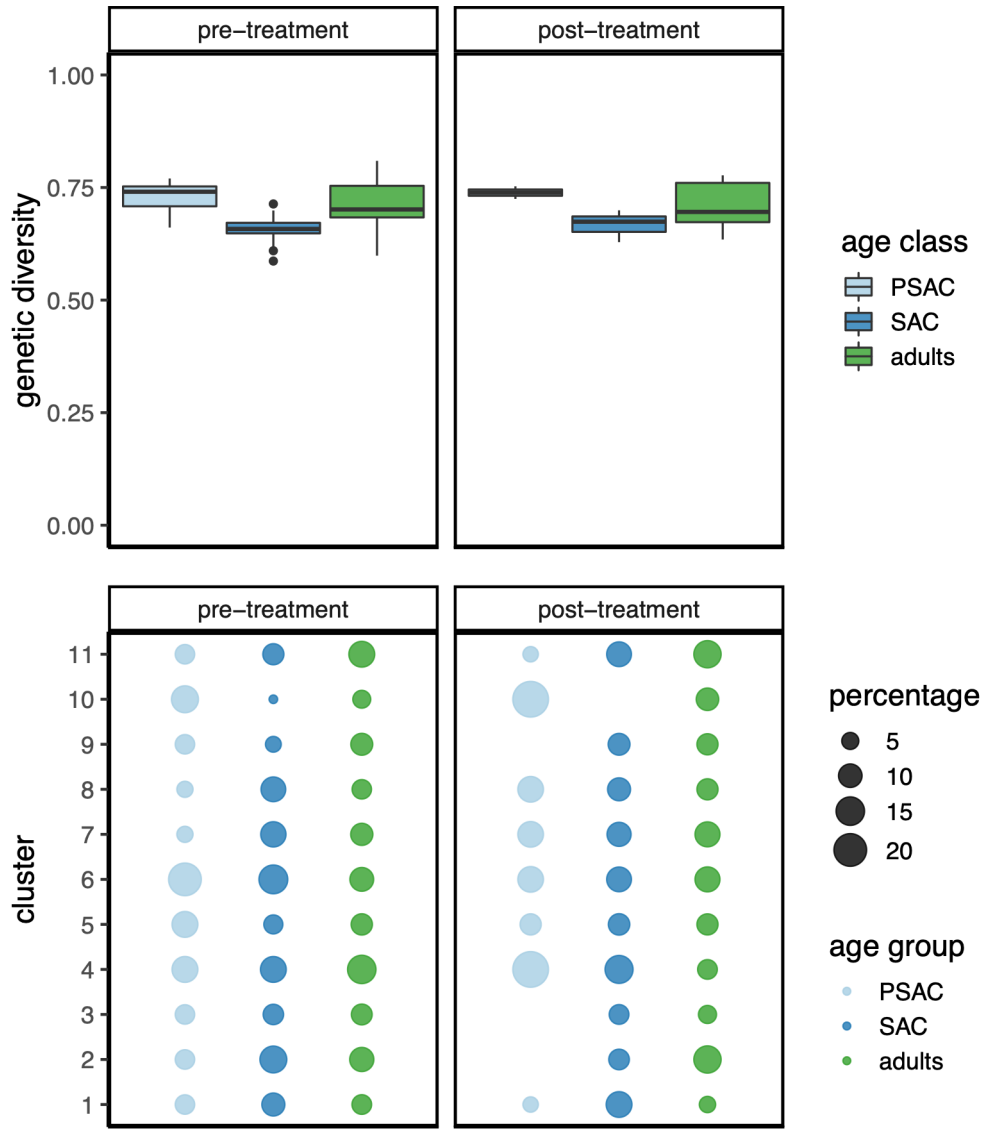

Figure 4. The population genetics of *Schistosoma mansoni* in PSAC, school children, and adults before and after praziquantel treatment. A. Genetic diversity is high in all age groups, although PSAC have significantly higher genetic diversity than SAC at both timepoints. B. Parasite populations fall within eleven genetic clusters. Adults are infected with parasites from all clusters both pre- and post-treatment, whereas SAC and PSAC are infected with a subset of the diversity. The size of the point reflects the percentage of miracidia isolated that fall into the genetic cluster.