

Age-related Worm Load and Worm Fecundity Patterns in Human Populations, as Indicated by Schistosome Circulating Antigens

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Recently, our group determined the relationship between serum CAA levels and fecal egg counts in two foci with very intense Schistosoma mansoni transmission: Maniema (Zaire), an area endemic for S. mansoni since several decades, and Ndombo (Senegal), where transmission has only been established since a few years. The objective was to study and compare age-related worm load and worm fecundity patterns in these two different endemic settings. Here, we will summarize the most important findings and conclusions of this study.

Key words: *Schistosoma mansoni* - circulating anodic antigen (CAA) - worm load - worm fecundity

To study the dynamics of schistosome infections, an accurate measure of worm burden is of major importance. However, due to their intra-vascular localization, *Schistosoma mansoni* worm numbers cannot be directly quantified in infected humans, and one has to rely on indirect methods, like the counting of eggs in feces (Katz et al. 1972, De Vlas & Gryseels 1992).

An alternative measure of schistosome infections is the detection of circulating anodic antigen (CAA) in serum (Deelder et al. 1989, 1994), which may provide a more direct assessment of worm loads than fecal egg counts. CAA is a glycoconjugate associated with the gut of the adult worm and released by the parasite in large amounts into the circulation of the infected host. CAA detection in serum appears to give a quantitatively stable diagnosis of *S. mansoni* infection (Polman et al. 1998). Several animal studies have shown a good correlation between worm loads and CAA levels (Deelder et al. 1994, Agnew et al. 1995).

By interpreting antigen levels as a direct reflection of worm load, it would be possible to describe the distributions and dynamics of *S. mansoni* infection in more depth than with egg counts only. Especially mechanisms like density-dependent fecundity and anti-fecundity immunity, could be very well studied by comparing antigen levels (representing worm load) and fecal egg counts in different endemic settings (Polman et al. 1995, Van Lieshout et al. 1995, Agnew et al. 1996).

Recently, by our group, the relationship between serum CAA levels and fecal egg counts was determined in two endemic settings with very intense *S. mansoni* transmission: Maniema (Zaire), an area endemic for *S. mansoni* since several decades, and Ndombo (Senegal), where transmission has only been established since a few years (Van Lieshout et al. 1997).

In both foci, it was examined whether CAA levels, as a direct measure of worm burden, confirmed the age-related pattern suggested by egg counts, and whether in the respective age groups the relation between CAA levels and egg counts suggested density-dependent fecundity.

Also, the relationship between CAA levels and egg output was compared between the two areas, to see whether this was influenced by the history of exposure on a population level. Due to the epidemic increase of schistosomiasis in Ndombo, most individuals had probably become infected within a relatively short time frame. In this situation history of infection should thus not be related to age, in contrast to the situation in Maniema (Gryseels et al. 1995). Also, according to the current hypothesis in which resistance develops only slowly after several years of infection, acquired immunity should still be absent in Ndombo, while present in Maniema (Butterworth et al. 1992, Gryseels 1994).

In the next paragraphs, we will give a summary of the most important findings and conclusions of this study, as described in detail by Van Lieshout et al. (1997).

Both datasets, Maniema (n=508) and Ndombo (n=246), were collected according to the same standardized methods with similar protocols of parasitological examination (i.e. two duplicate 25 mg Kato-slides) and circulating antigen determination

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(Polderman et al. 1985a, b, Stelma et al. 1993, Polman et al. 1995, Van Lieshout et al. 1995, 1997).

Based on fecal egg counts, *S. mansoni* infection levels were found to be extremely high and remarkably similar in both communities. In contrast to egg counts, CAA levels differed significantly between the two groups. Mean CAA levels were higher in Maniema than in Ndombo, also after stratification into separate egg count classes.

Both communities showed the characteristic age-related pattern of egg counts, except for a more pronounced peak in Ndombo in the age group of 10-14 years. Likewise, CAA levels showed a rapid increase in young children and a peak level around 5-15 years in both populations, but thereafter antigen levels decreased in the Ndombo population to a much lower plateau. This sharp drop of CAA levels in adolescents from Ndombo, suggests comparatively higher worm fecundity in adult hosts in this recent focus.

For more detailed comparison, both communities were divided into four age groups and regression analysis was performed. In both populations, the relationship between CAA levels and egg counts was found to be nonlinear, i.e. at high antigen levels, egg counts were not as high as expected in case of a linear relationship. This agrees with the theory of density-dependent fecundity, i.e. a decreased egg production by female worms in the case of high worm loads (Medley & Anderson 1995). However, the phenomenon of density-dependent fecundity is still a point of debate (Wertheimer et al. 1987, Gryseels & De Vlas 1996).

In Maniema, the relationship between CAA levels and egg counts was found to be constant at different age groups, indicating that the reduction in egg counts seen in adults after a peak during adolescence is caused by a genuine reduction in worm burden rather than reduced worm fecundity with age of the host. However, in Ndombo, significant differences were found between age groups. This effect of age seemed to be a combination of several factors, not clearly attributable to one parameter.

The differences that were found in the relation between CAA levels and egg counts after comparison of the two groups, suggest that in case anti-fecundity immunity would be of any importance in *S. mansoni* infections, it seems to be more related to the history of transmission for the total population, than to exposure experience on an individual level. We have no explanation for the fact that worm fecundity in young children from Ndombo seems to be relatively low compared to adults in this area and is more similar to the Maniema population.

All these findings are based on the assumption that serum CAA levels do reflect actual worm loads, irrespective of the intensity of infection or the immune status of the host (Agnew et al. 1995). Still, it can not be ruled out that the production and/or clearance of CAA is affected by several, in part host-related, mechanisms (Van Lieshout et al. 1995). For example, the efficiency of the immune system to clear CAA may be influenced by age or health status of the host, as well as by previous experience of infection. Alternatively, the production of CAA may depend on geographical strain differences of the parasite, or the age of the worms. To gain a better understanding on the mechanisms of production and/or clearance of antigens, more research on these issues is definitely needed.

In conclusion, estimation of worm burdens in humans by serum CAA determination appears to be a valuable approach, which can provide important complementary information on the dynamics of *S. mansoni* infections in humans.

At this moment, we are also collecting CAA detection results from other *S. mansoni* endemic areas, in order to study the relation between worm burdens and egg production in each specific endemic situation, as well as on a comprehensive level.

We are also trying to include circulating antigens in a mathematical model based on egg counts, as developed by De Vlas et al. (1992). In this way, we intend to study the relation between worm burdens, antigen levels and egg counts in a more refined way, than has so far been possible through regression analysis.

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