Adult resistance to schistosomiasis mansoni: age-dependence of reinfection remains constant in communities with diverse exposure patterns

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SUMMARY

In a fishing community on Lake Albert in Uganda the pattern of intensity of *Schistosoma mansoni* infection 6 months after treatment with praziquantel was found to be very similar to reinfection patterns seen in previously studied endemic communities: the profile peaks sharply at around the age of 10 years falling away rapidly to much lower levels in adults. This is in stark contrast to the patterns of water contact, which differ greatly between fishing and non-fishing communities. On Lake Albert, adults appear to be more heavily exposed than children. From these observations we conclude that adults are physiologically (perhaps immunologically) more resistant to infection after treatment than children.

Key words: schistosomiasis, immunity, age-intensity profile, water contact.

INTRODUCTION

The extent to which the lower levels of schistosomiasis infection in adults is due to acquired immunity or reduced contact with water containing infected vector snails has long been debated (Warren, 1973; McCullough & Bradley, 1973; Butterworth, 1994; Gryseels, 1994). Many studies have reported a reduction in water contact with increasing age (Dalton & Pole, 1978; Wilkins *et al*. 1987; Fulford *et al*. 1996*a*; Stelma, 1997). While several attempts to relate reinfection intensity to age and exposure have been made, they have always been compromised by the difficulty in estimating exposure (Butterworth *et al*. 1988; Bundy & Blumenthal, 1990; Fulford *et al*. 1996*b*). In this study, we examined reinfection and water contact in a community on Lake Albert, Uganda, where the fishing economy leads to high levels of adult water contact. Although the contact patterns on Lake Albert and those observed previously in non-fishing communities could hardly be more different, their reinfection profiles are almost indistinguishable. This finally places beyond dispute the conclusion that innate or acquired immunity to *Schistosoma mansoni* increases dramatically as children become adults.

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Patterns of mean infection intensity (assessed by egg excretion) with age in endemic communities prior to intervention are difficult to interpret because they reflect the cumulative worm burden acquired over many years. Profiles of reinfection after chemotherapeutic cure, on the other hand, reflect current rates of parasite acquisition and are remarkably constant. The 3 reinfection profiles for *S. mansoni* in Kenya shown in Fig. 1 are typical of other published data for this species (Stelma, 1997; Demeure *et al*. 1993). Fewer data are available for *S. haematobium* and *S. japonicum* but these also appear to conform to the *S. mansoni* pattern (Wilkins *et al*. 1987; Wu *et al*. 1994).

Age-related patterns of water contact have been widely reported, although only 6 studies explicitly analyse reinfection patterns with respect to both water contact and host age (Wilkins *et al*. 1987; Chandiwana, Woolhouse & Bradley, 1991; Demeure *et al*. 1993; Wu *et al*. 1994; Etard, Audiberta & Dabo, 1995; Stelma, 1997). These all used regression techniques (either logistic or least squares) to demonstrate an apparent reduction in reinfection among older people beyond that accounted for by exposure. However, statistical problems arising from the inaccuracy and imprecision of exposure estimates cast doubt on the validity of this conclusion. The unknown risk of infection due to the different activities engaged in by adults and children may overestimate adult exposure relative to children's (Bundy & Blumenthal, 1990; Fulford *et al*. 1996*a*;

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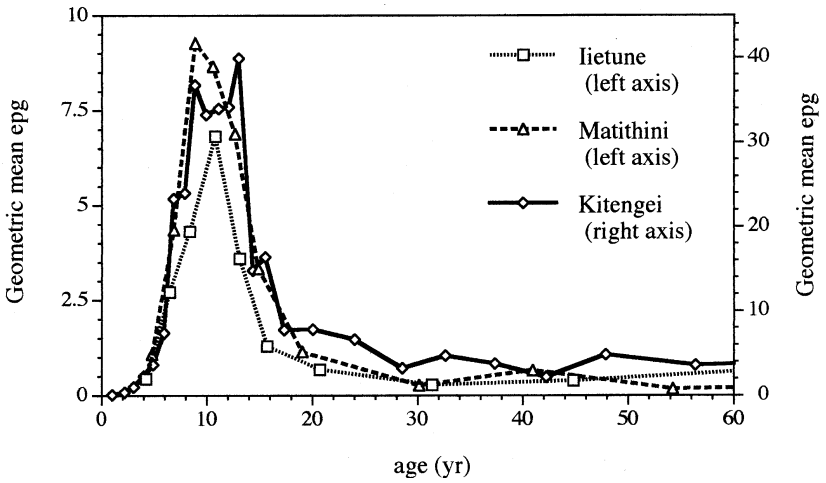

Fig. 1. Geometric mean reinfection intensities (eggs per gram faeces) *versus* age for Kenyan communities (adapted with permission from Fulford *et al.* 1998).

Butterworth *et al.* 1988) while imprecision in estimates of individuals' exposure, even without systematic bias, leads to incomplete removal of the influence of (age-dependent) behaviour in the regression analysis (Fulford *et al.* 1996*b*). Since most previous investigations were done in rather similar situations, in which domestic rather than economic activities dominate adult water contact, all may suffer a similar abrupt reduction in exposure between childhood and adulthood, mirroring the commonly observed reinfection pattern. We therefore chose to study an area in which contact with water was related to occupation in the expectation that the pattern of contact would contrast strongly with those previously observed and would not confound other age-related influences on infection rates. An earlier study (Wu *et al.* 1994) of reinfection in a fishing community involved a more heterogeneous economy in which adult water contact did not predominate.

METHODS AND STUDY POPULATION

Field studies were carried out in Butiaba village, adjacent to Lake Albert, Masindi district, Uganda, where conditions are unsuitable for agriculture and the entire community is involved in the fishing industry. The total population size was 2331. A random sample of 574 people aged between 5 and 54 years were involved in the reinfection study, although water contact observations were made on the whole population.

All study members, irrespective of infection status, received 2 doses of praziquantel, 40 mg/kg, 6 weeks apart. Efficacy of chemotherapy was assessed 6 weeks after each treatment. Stool examinations were performed prior to treatment and 3 and 6 months after treatment with the second dose. At each time-point levels of *S. mansoni* infection were estimated by counting eggs on two 50 mg Kato slides prepared from each of 3 stools. A final stool survey, 1 year after treatment and (re)treatment of the community is currently in progress.

Observations of water contact were made every other day over a period of 4 months, following methods used earlier in Kenya (Fulford *et al.* 1996*a*). Two observers, recruited and trained locally, worked a carefully balanced rota of 6 h shifts covering the daylight hours. Name, age, sex, site, time, activity and degree of immersion were recorded for each contact.

Snail collections were made twice per month over a 2 year period using the method of Ouma *et al.* (1989).

The 95% confidence interval for the age of peak reinfection was estimated for each community by considering 20 bootstrap samples from the original data. Each bootstrap sample was stratified into between 15 and 20 approximately equal-sized age groups (the exact number chosen randomly for each sample) and smoothed using an autoregressive model with 7 effective degrees of freedom (Ouma *et al.* 1998; Mollie, 1996). The peak age of each sample was estimated by the mean age of the stratum within which the smoothed intensity was greatest. The 95% confidence intervals were calculated from the mean ± 2 S.D. of the 20 sample estimates.

RESULTS

Butiaba, the village upon which this study was centred, lies on a spur of land projecting into Lake Albert. Water contact occurred in the swamp to the north of the village, along the open beach to the west, and in the shallow fishing waters behind the swamp. Infected snails were recovered throughout the study period, especially from the northern shore (*Biomphalaria sudanica*) and the shallow fishing waters (*B. stanleyi*): 6·8% of the 4584 *B. stanleyi* and 4·4% of 4063 *B. sudanica* snails recovered from the contact

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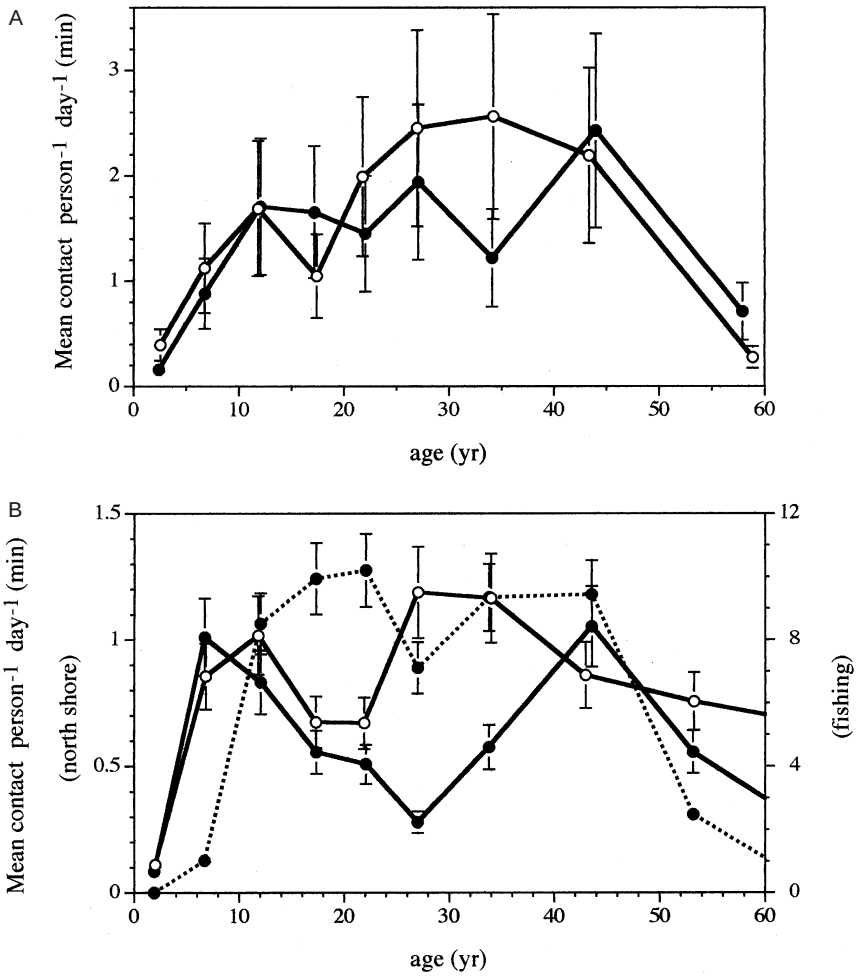

Fig. 2. Arithmetic mean (±S.E.) observed water contact per person in Butiaba. (A) Western shore; (B) northern shore and fishing ground. (○) Females; (●) males; (——) shore; (----) fishing ground.

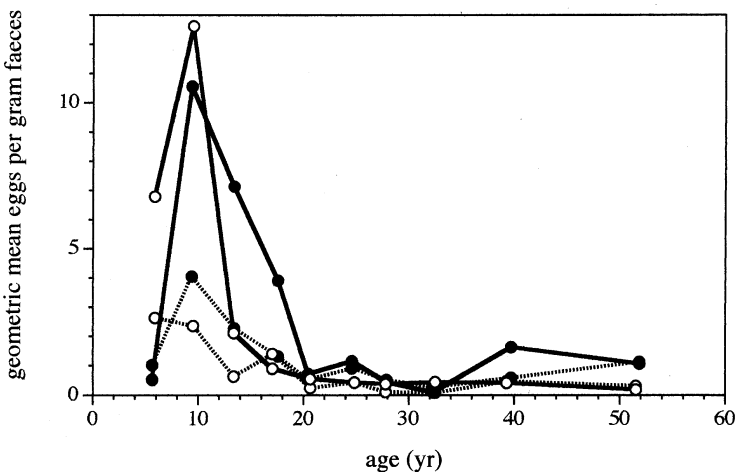

Fig. 3. Geometric mean reinfection intensities (eggs per gram faeces) *versus* age for Butitaba. (○) Females; (●) males; (——) 6 month post-treatment; (----) 3 month post-treatment.

sites were found to be shedding *S. mansoni* cerariae. On the western beach both male and female water contact rose to a plateau in adulthood, only falling away in old age (Fig. 2A). Contact on the northern shore was a little more complicated. Women had more contact with water than girls, a mixture of domestic activities and fish trading, but were almost never seen in the fishing waters (Fig. 2B). Young adult males were less apparent on the northern shore but 'reappeared' in middle age. Observations from boats revealed that these absent young men were heavily engaged in fishing on the outer fringes of the swamp, not visible from the shore, where they were extensively exposed to infective water (Fig. 2B).

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Very similar patterns resulted when allowance was made for the use of soap (weighted zero) or degree of immersion (weighted 1, 2 or 3 according to the number of body parts exposed or 5 for whole body immersion).

Prior to treatment the geometric mean intensity was 233 eggs/g faeces (epg) and the 3-stool prevalence 90·5 %. The patterns of reinfection at 3 and 6 months after treatment are shown in Fig. 3. A number of individuals (20·0 %) were removed from the analysis because they were still excreting a small number of eggs ($\geqslant$ 5 epg) even after the second dose of praziquantel. The 95 % confidence interval for the age at which reinfection intensity peaked in the Butiaba cohort was 10·3 to 13·7 years. This does not differ significantly ($X^2 = 1{\cdot}95$ on 1 D.F.; $P > 0{\cdot}05$) from the 3 Kenyan communities shown in Fig. 1A (7·4 to 12·6 years in Kitengei, 8·0 to 11·7 years in Iietune and 8·1 to 12·5 in Matithini). The reinfection intensity peaks were also very similar in breadth in all 4 communities.

DISCUSSION

These observations demonstrate that the patterns of behaviour and exposure with age in Butiaba are very different from those seen in Kenya and elsewhere. Overall, both male and female contact activities were greater in adults than in children, and the patterns were little affected when allowance was made for the degree of immersion or the use of soap, factors which had complicated earlier studies (Bundy & Blumenthal, 1990; Fulford *et al*. 1996*a*). In fact, soap was very rarely used in the lake while the degree of immersion was much less age dependent than was observed in Kenya.

In contrast, intensities of reinfection 6 months after treatment showed a pattern typical of other studies, with a peak at around 10 years of age, falling away to much lower levels in adults. Levels of infection 6 months after treatment were still quite low and, since pre-treatment intensities had been moderately high, treatment failure would obviously have greatly interfered with the results. For this reason a fairly stringent criterion was used to define treatment failure. Treatment failure, as is commonly observed, followed a similar pattern to that of reinfection so a disproportionate number of those omitted for this reason were children. It can therefore be safely concluded that the lower rate of reinfection among adults relative to children was not an artefact brought about by the removal of these individuals. The obvious, and highly significant, rise in egg counts between the 3 and 6 month surveys confirms that the pattern at 6 months post-treatment was genuinely the result of reinfection, rather than residual infection that praziquantel had failed to clear.

Since behaviour alone cannot explain the similarities of reinfection profiles, there must be a strong age-dependent resistance to (re)infection which changes abruptly in the teenage years. Whether this immunity is purely innate or has an acquired component cannot be resolved by the present study, although studies on immunology (Hagan *et al*. 1991; Rihet *et al*. 1991; Dunne *et al*. 1992) and genetics (Marquet *et al*. 1996) of the disease point to a role for acquired immunity. Immunological studies of populations in which adult resistance to infection is not strongly confounded by lack of exposure promise to be more revealing. Cellular and humoral studies have therefore been initiated in Butiaba.

The age of peak infection intensity in populations prior to intervention has been observed to correlate negatively with the average intensity in the population (Woolhouse *et al*. 1991; Fulford *et al*. 1992). This 'peak shift' is predicted by models of schistosome population dynamics which include acquired immunity (Woolhouse *et al*. 1991) but may also arise due to non-immunological phenomena (Fulford *et al*. 1992, 1996*b*). There is no evidence for such changes in peak position in the available reinfection data, but minor shifts could be accommodated by the above argument.

Controlling schistosomiasis in endemic areas requires repeated administration of expensive drugs such as praziquantel or oxamniquine, which is beyond the means of many developing countries where the disease is most prevalent. Much research effort has therefore been directed towards understanding the immunology of this infection in the hope that a vaccine might be developed. An understanding of why adults are less heavily infected than children should not only shed light on this question but would also assist in the planning of control programmes.

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