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Exploring the impact of infection-induced immunity on the transmission of *Schistosoma japonicum* in hilly and mountainous environments in China☆

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ABSTRACT

Schistosomiasis has long been a threat to villagers in hilly and mountainous areas of southwestern China where the intermediate snail host is abundant. In recent years our group has focused on the development and parameterization of a community-level mathematical model of *S. japonicum* transmission that accounts for the role of environmental determinants of transmission intensity in Sichuan Province. To date the model has not incorporated acquired immunity. A review of previous epidemiologic data from our study area in Sichuan suggested modeling of acquired immunity as a function of history of infection. To explore the potential impacts on the dynamics of transmission, a mathematical representation of acquired immunity was incorporated, and parameterized based on this epidemiological evidence. It is shown through simulation that the effect of immunity is to reduce the rate of worm development and thereby lower the endemic level significantly. The effect was more striking at increasing levels of a village'tm)s basic reproductive number. Further, residual immunity modestly alters the threshold of external parasite input necessary to trigger re-emergence of transmission and its subsequent rate of development. Despite limitations in our quantitative knowledge of the immunity function, these findings, along with the uncertainties in transmission dynamics at low infection levels, underscore the need for improved diagnostic methods for disease control, especially in potentially re-emergent settings.

1. Introduction

Schistosomiasis is one of the most prevalent parasitic diseases in tropical and subtropical regions of the world (Steinmann et al., 2006; Rollinson et al., 2012). In China, tremendous effort has been devoted to disease control, reducing the number of infections by more than 90% during the past six decades (Zhou et al., 2007). However, as recently as 2007, there were still estimated to be over 700,000 infected people in seven provinces (Wang et al., 2009). Among these, we concentrate our studies on Sichuan Province, where transmission persists mainly in hilly and mountainous environments which, while typical in southwest China, presents significant ecological differences when contrasted to the marshland and plain environments in lower Yangtze River regions. In Sichuan, human–environment interactions are central to schistosome transmission (Spear et al., 2004a). On one hand, the natural environment, including climate conditions such as temperature and precipitation, and geographical conditions such as surface water networks and habitat areas, dominate the development, migration and distribution of the intermediate host snails and both free-swimming stages of schistosomes in water (Spear et al., 2004b; Gurarie and Seto, 2009). On the other hand, it is human behaviour that initiates the asexual phase of transmission by contacting contaminated water, becoming infected, and subsequently introducing egg-containing faeces into the environment (Liang, 2003; Liang et al., 2005).

In order to quantify the impacts of these diverse factors on disease transmission, our group has devoted considerable effort to the development and parameterization of village-level mathematical models. These models have been utilized to assess the effect of various control strategies by predicting long-term infection patterns under multiple scenarios (Liang et al., 2005, 2007; Liang and Spear, 2008). However, these models have not incorporated the potential effects of human immunity to infection for which there has been increasing evidence in other settings. Here we present suggestive evidence of the existence and magnitude of acquired immunity from both the literature and from a re-analysis of our earlier epidemiological data and then evaluate its epidemiological

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implications through a simplified version of our previous models now including the effects of immunity.

Epidemiological studies have shown that people living in areas endemic for schistosomiasis are able to gain some resistance against further infection, implying the existence of acquired immunity (Mutapi et al., 1997; Ross et al., 2000). However, it is still controversial what factors are most relevant to the development of immunity. In some setting there is evidence of age-dependent immunity which suggests that older people are less susceptible to infection than the young who are similarly exposed (Ross et al., 2000). Alternatively, others have addressed the possibility of infection-induced immunity which suggests that immunity is induced and accumulated by previous infection history (Anderson and May, 1991). Evidence for both hypotheses will be reviewed next.

1.1. Age-dependent immunity

Earlier observational studies have suggested that age-dependent infection patterns exist, but these generally lacked any control for exposure (Kloetzel and da Silva, 1967). Others attempted to detect age-dependent immunity in studies involving treatment of all participants initially, and then compared the re-infection level and the intensity of water exposure during the same time interval for different age groups. Following this design, evidence of age-dependent immunity was provided by studies of *S. mansoni* infection among a group of schoolchildren in Kenya, although the age range of the participants was quite limited (Sturrock et al., 1983). More evidence was subsequently found for both *S. mansoni* and *S. haematobium* in Africa (Wilkins et al., 1987; Kabatereine et al., 1999). For *S. japonicum*, age-dependent immunity was first suggested from a study in the marshland regions surrounding Poyang Lake, China (Wu et al., 1994). A study later conducted in a similar environment in China also found a negative relationship between infection and exposure in different age categories (Ross et al., 2000). However, it should be noted that human exposure was assessed by only water contact intensity. Few of these studies measured cercarial risks which are related to infection in a more direct way.

1.2. Infection-induced immunity

Infection-induced immunity to helminthes has been incorporated in mathematical models (Berding et al., 1987; Michael et al., 2001; Gambhir and Michael, 2008). The theory is based on two key assumptions: (1) protective immunity increases as a function of cumulative experience of infection and (2) the rate of increase of protection at any time is proportional to the current intensity of infection (Anderson and May, 1991). It follows that the higher the cercarial exposure, the more quickly immunity will develop. Therefore, in two populations exposed at different levels, peak infection intensity will occur earlier after infection begins in the population with the higher exposure. Hence, the "peak shift" pattern, shown in Fig. 1, is consistent with infection-induced immunity (Anderson and May, 1985; Woolhouse, 1998).

In an early experiment designed to confirm this pattern, Crombie and Anderson exposed mice to four different levels of cercariae of *Schistosoma mansoni* and tracked their infections for months (Crombie and Anderson, 1985). It was shown that the mean worm burden peaked and then declined at a much earlier stage (around 8 weeks after exposure) in the group with the highest exposure, compared to the second highest exposed group where the peak occurred much later (around 17 weeks after exposure). In the two least-exposed groups, on the other hand, worm burden continuously increased without declining.

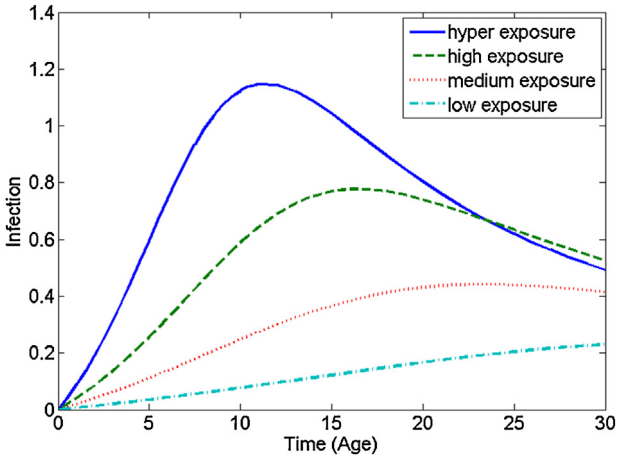

Fig. 1. A typical pattern of peak-shift with hypothetical data.

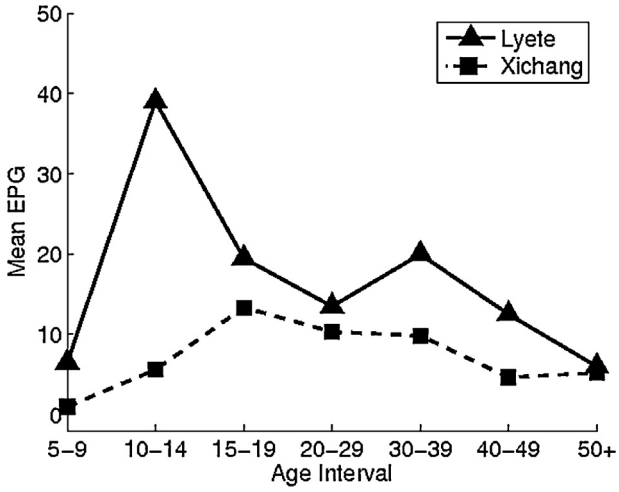

Fig. 2. Infection versus age classes of two populations. Corresponding to different infection levels of *S. japonicum*, the two groups were respectively from Lyete, Philippines [solid line, data acquired and redrawn from Acosta et al. (2002)] and Xichang, China.

Similar trends have been suggested by epidemiological data. In a study where age-infection patterns of *Schistosoma haematobium* in two endemic areas in Zimbabwe were tracked, Mutapi et al. found that the infection rate in a population was negatively correlated with the age stratum at which the peak level of infection was observed (Mutapi et al., 1997). Specifically, the 5–9 age stratum was most infected in the higher endemic area while in the lower endemic area it was the 10–14 age stratum, which is again consistent with the "peak shift" pattern.

This pattern can also be seen by comparing the infection data from our study in Sichuan and the survey conducted by Acosta et al. in Leyte, Philippines (Acosta et al., 2002). Both populations had been treated using mass chemotherapy two years prior to the collection of re-infection data. Thus, both datasets reflected re-infection rates during roughly the same time interval. Shown in Fig. 2, peak infection intensity was found in the 10–14 age stratum in Leyte and the 15–19 age stratum in Xichang, with much higher levels of infection in the former.

2. Preliminary analysis

Earlier data from our Sichuan studies allows an exploration for suggestive evidence of age-induced versus infection-induced immunity. The data used here were collected between 2000 and