New Insights into the Observed Age-Specific Resistance to Reinfection with *Schistosoma japonicum*

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(See the article by Kurtis et al. on pages 1692–8)

In this issue of *Clinical Infectious Diseases*, Kurtis and colleagues [1] present a longitudinal study of a population in the Philippines chronically exposed to *Schistosoma japonicum*. Past studies of such field populations have demonstrated that resistance to reinfection with this parasite can be observed after 14 years of age and that resistance continues into adulthood [2, 3]. A Kaplan-Meier analysis of the time to reinfection following curative chemotherapy is shown in figure 1, originally published in *Journal of Infectious Diseases* 10 years ago, showing the same communities in which this current study [1] was performed. Prior exposure to schistosomes induced no resistance to reinfection in younger individuals, but individuals aged 14–35 who were infected and then cured had a modest prolongation in their time to reinfection, compared with uninfected control subjects. Statistically, this benefit from past infection could no longer be demonstrated after 2–3 years and was presumed to be relatively short lived [2] (figure 1).

It has long been assumed that this phenomenon was caused by the slow development of immunity in these populations chronically exposed to the parasite. The study by Kurtis et al. [1] presents an intriguing and provocative alternative explanation: the increased resistance over time is, in part, mediated by the rise in sex hormones associated with puberty. The idea that nonimmunologic factors might participate in the observed age-related resistance to *Schistosoma* infection is relatively new. Recent studies from communities newly exposed to schistosomiasis in Africa [4] also showed that older ad-
olescents and adults were less-intensely infected than younger children. Is this because of decreased water contact or other factors?

Those in the field of schistosomiasis research have long been interested in resistance to reinfection in humans in the hope that insights into its mechanism(s) would lead directly to vaccine development [5]. Despite the availability of a nontoxic oral drug that is effective against all species of *Schistosoma* (praziquantel) and its broad application in chemotherapy-based national control programs, schistosomiasis remains a significant public health problem in the world [6]. This is, in part, because of rapid reinfection after curative chemotherapy and, in part, because of the increased prevalence of schistosomiasis in sub-Saharan Africa. The latter issue is primarily caused by water resource development along several major African rivers and lakes. In addition, we now recognize that periodic chemotherapy reduces the prevalence of end-organ fibrosis induced by decades of infection but does not eliminate the more subtle and far more common morbidities, such as anemia, growth stunting, decreased cognitive development, and decreased functional work capacity. To significantly reverse all negative effects of infection, we desperately need both cheap drugs and a vaccine that slows or blocks reinfection [3, 5].

We can protect experimental animals through vaccination with irradiated cercariae. Cercariae are the infective larval forms of the parasite released by infected snails that penetrate human skin and evolve into adult worms in the infected host. It has been harder to demonstrate in experimental animals the protective effect of past natural infection followed by curative chemotherapy. Most of the human evidence for resistance to reinfection comes from the careful study of human populations chronically exposed to one of the *Schistosoma* species that causes human infection. These studies have suggested that children 12–14 years of age develop partial resistance to reinfection, compared with younger individuals residing in the same area. The precise nature of this acquired resistance is unknown, but it has been the subject of intense investigation for >2 decades. Most investigators in the field have assumed that chronically infected humans develop resistance slowly over time, that this type of resistance is immunologically mediated, and that it is directed toward the invasive larval forms of the worm. Most of the evidence for these concepts comes from animal studies with mice, rats, and primates. The immunologic basis for human resistance has also been supported by studies that show strong correlations between specific immunologic responses and decreased reinfection over time. Such correlative evidence, however, can only be confirmed through active vaccination trials in humans [7].

As a result, schistosomiasis researchers worldwide have developed several highly purified antigens as potential vaccine candidates over the years. All have been tested in animal models, and some have been tested in primates [8, 9]. They have performed immunologic correlate studies similar to those outlined in the study by Kurtis et al. [1] using these highly purified molecules in vitro and serum or lymphocyte samples from human populations chronically exposed and periodically naturally reinfected with *Schistosoma* species [9]. One such molecule is already in a phase-2 vaccine trial in West Africa.

Kurtis and colleagues [1] have added a new dimension to our thinking. They have shown that increased levels of the pubertal hormone dehydroepiandrosterone sulfate in humans exposed to *S. japonicum* is associated with reduced reinfection over time. This is exactly the type of correlative data that has been used to support the immunologic hypothesis. Does this mean that resistance to schistosomes is all about hormones and that science has been “barking up the wrong tree” for >2 decades? I can recall a notation on the January 1992 cover of *Scientific American* asking, “Did sex evolve as a defense against parasites?” [10]. Not at all. In the authors’ own discussion, they point out that dehydroepiandrosterone sulfate is a potent immune modulator, including up-regulation of Th2-driven antibody production and down-regulation of proinflammatory cytokines. Perhaps puberty brings with it the enhanced ability to mount an effective protective immune response against schistosomes. Alternatively, dehydroepiandrosterone sulfate levels and puberty may turn out to be markers of yet other immunologically or nonimmunologically based factors, such as increased skin thickness or enhanced fat deposition, either of which could decrease the efficacy of schistosome maturation in humans.

Clearly, more studies are needed to follow up on this observation.

The idea that hormones play a role in resistance to infection is not a new concept in experimental animals [11]. The prevalence and intensity of a wide variety of nematodes, trematodes (including schistosomes), cestodes, and protozoa are different between the sexes. Not all of these differences can be explained by differences in exposure. Sex hormones can affect the parasites and the host immune response to them, and parasitic infection can also affect hormone production by the host. This interaction between sex hormones and infection has been studied for several decades in experimental animals, but this study by Kurtis et al. [1] represents one of the first longitudinal studies in humans chronically infected with schistosomes.

This article strongly suggests that human vaccine trials for *Schistosoma* infection must eventually be done in preadolescent children living in countries of endemicity. They currently suffer disproportionately from this infection, and, as this and many other studies have shown, they are more likely to be rapidly reininfected after curative chemotherapy. We should also look carefully at the immune responses and vaccine efficacy in both sexes pre- and post-adolescence. Why do older children and adults appear to be
more resistant to reinfection after puberty? Is it immunity or is it hormones? The answer is likely both, as well as several other as-yet undefined factors.

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References