

Increases in Levels of Schistosome-Specific Immunoglobulin E and CD23⁺ B Cells in a Cohort of Kenyan Children Undergoing Repeated Treatment and Reinfection with *Schistosoma mansoni*

Carla L. Black,¹ Erick M. O. Muok,³ Pauline N. M. Mwinzi,³ Jennifer M. Carter,¹ Diana M. S. Karanja,³ W. Evan Secor,² and Daniel G. Colley¹

¹Center for Tropical and Emerging Global Diseases and Department of Microbiology, University of Georgia, Athens, and ²Division of Parasitic Diseases, Centers for Disease Control and Prevention, Atlanta, Georgia; ³Centre for Global Health Research, Kenya Medical Research Institute, Kisumu, Kenya

Background. Age prevalence curves for areas in which schistosomiasis is endemic suggest that humans develop partial immunity to reinfection beginning in early adolescence. We conducted a 2-year longitudinal study to determine whether children infected with *Schistosoma mansoni* develop protection-related immune responses after treatment with praziquantel and whether the development of these immune responses is accelerated by frequent treatment after reinfection.

Methods. Children (8–10 years old) were tested for *S. mansoni* every 4 months and treated with praziquantel when positive (arm A; *n* = 68) or were tested and treated at the end of the 2-year follow-up period (arm B; *n* = 49).

Results. Children in arm A who remained free of infection during follow-up had significantly higher baseline levels of schistosome-specific immunoglobulin E (IgE) than did children with ≥ 2 repeat diagnoses of *S. mansoni* infection. Children with ≥ 2 repeat diagnoses of *S. mansoni* infection had significantly increased levels of anti-schistosome IgE and CD23⁺ B cells after receiving ≥ 3 praziquantel treatments over the course of follow-up. No increase in either parameter was seen in children who received only the baseline praziquantel treatment.

Conclusions. B cell activation and anti-schistosome IgE are associated with resistance to *S. mansoni* in children, and these immunological parameters can be increased by multiple rounds of infections and praziquantel-induced cures.

Schistosoma mansoni age prevalence curves for areas of endemicity suggest that intensity and prevalence of infection peak during the early teenage years. Prevalence then plateaus while infection intensity sharply declines as individuals enter the third decade of life. Immunologic studies suggest that the decline in intensity is in part attributable to the development of immunity to new infections [1–3]. Given that the life span of *S. mansoni* worms is ~5–10 years [4, 5], this resistance to

reinfection coincides with the time when worms from the initial infection begin to die. These findings have lead to the hypothesis that worm death, rather than worm maintenance, is responsible for inducing resistance to reinfection [6]. We have previously shown that male adults occupationally exposed to *S. mansoni* developed increased resistance to reinfection after

Potential conflicts of interest: none reported.

Presented in part: 58th Annual Meeting of the American Society for Tropical Medicine and Hygiene, 18–22 November 2009, Washington, DC (abstract 381).

Financial support: National Institute of Allergy and Infectious Diseases (Public Health Service grants R01 AI053695 to D.G.C. and T32 AI060546 to C.L.B.) and Fogarty International Center (grant D43 TW007123 to P.N.M.M.), National Institutes of Health; Centers for Disease Control and Prevention (support to W.E.S.); Kenya Medical Research Institute (support to E.M.O.M., P.N.M.M., and D.M.S.K.).

Disclaimer: The findings and conclusions in this report are those of the authors and do not necessarily represent the views of the Centers for Disease Control and Prevention.

This work is published with the permission of the director of the Kenya Medical Research Institute.

Received 4 November 2009; accepted 8 March 2010; electronically published 18 June 2010.

Reprints or correspondence: Daniel G. Colley, Center for Tropical and Emerging Global Diseases, 500 D. W. Brooks Dr, Coverdell Center, Room 145, University of Georgia, Athens, GA 30602-3799 (dcolley@uga.edu).

The Journal of Infectious Diseases 2010;202(3):000–000

© 2010 by the Infectious Diseases Society of America. All rights reserved.

0022-1899/2010/20203-00XX\$15.00

DOI: 10.1096/653828

repeated cycles of treatment, reinfection, and retreatment [7].

The most consistent immune parameter associated with resistance to reinfection is increased levels of schistosome-specific immunoglobulin E (IgE) [8–11]. B lymphocytes are the producers of all immunoglobulins, including IgE, and we recently reported an association between the CD23⁺ B cell subset and increased resistance to reinfection in our cohort of male adults [12]. CD23 is the low-affinity IgE receptor (FcεRII), and its expression on B cells is in part considered an indication of their maturity [13]. CD23 binds to a variety of membrane and soluble molecules—such as CD21, CD11b, CD11c, and IgE—and in its soluble form can act as a B cell proliferation factor [14]. The functional roles of the a and b isoforms of membrane-bound and soluble CD23 include B cell development, IgE binding, cell adhesion, antigen presentation to T cells, and regulation of IgE synthesis [15–19].

It has been postulated that resistance to reinfection can develop sooner than early adolescence in areas where endemicity is high or where there are programs leading to the early treatment of infections in children [20–22]. World Health Assembly resolution 54.19 recommends periodic mass treatment of children with the drug praziquantel in areas where schistosomiasis is endemic. Although intended to control morbidity, the periodic killing of adult worms might have the additional benefit of hastening the development of resistance to reinfection by inducing premature worm death. However, the appropriate interval at which treatment should be given to control morbidity or enhance resistance to reinfection has not been extensively evaluated in different epidemiologic settings. The purpose of the present study was to determine whether 8–10-year-old children infected with *S. mansoni* develop protective immune responses after treatment with praziquantel and whether the development of these anti-schistosome immune responses is accelerated by more frequent treatment over a 2-year period.

METHODS

Study Population

All subjects began the study as 8–10-year-old children recruited from 8 primary schools located within 3 km of Lake Victoria in the Asembo Bay area of the Nyanza Province in western Kenya. *S. mansoni* is highly endemic in the area. A 2001 survey of schools in the area found that the prevalence of *S. mansoni* ranged from 35%–80% [23].

After an initial screening of 485 children, 155 of the 179 children who were positive for *S. mansoni* were enrolled in a 2-year longitudinal study. Children were assigned into treatment arm A ($n = 88$) or treatment arm B ($n = 67$). Assignments were made by school except in the case of one school, which had the largest number of students and the highest *S. mansoni* prevalence. Students in this school were randomized to arm A or B. The final study population consisted of 68

children from arm A (77.3%) and 49 children from arm B (73.1%) who completed the 2 years of follow-up.

Study Procedures

In the baseline survey, all consenting children aged 8–10 years attending the study schools were tested for the presence of *S. mansoni* eggs by the Kato-Katz method, using 2 slides from a single stool sample. Children positive for *S. mansoni* were then asked to enroll in a 2-year longitudinal study and assigned to arm A or B as described above. At baseline and each follow-up visit, children provided a stool sample for testing for *S. mansoni* eggs as well as *Ascaris lumbricoides*, hookworm, and *Trichuris trichiura* by the Kato-Katz method, again using 2 slides from a single stool sample. Blood samples were also obtained from children by venipuncture for immunological analysis as well as testing for malaria parasitemia via Giemsa-stained blood smears. Children infected with *S. mansoni*, soil-transmitted helminths (STHs), or *Plasmodium falciparum* were treated with praziquantel (40 mg/kg), albendazole (400 mg), or artemether-lumefantrine (Coartem [Novartis]; 6 doses administered over 3 days), respectively.

Children in arm A were tested and treated every 4 months, for a total of 6 follow-up visits after baseline testing. Children in arm B were tested and treated only at baseline and again at the end of the 2-year follow-up period.

At study entry, a short questionnaire was administered to students in both study arms in which they were asked to characterize how often they went to the lake to engage in such activities as bathing, swimming, or fishing as one of the following: almost every day, sometimes (once a week), rarely (once a month), or never. A similar questionnaire was administered to the parents regarding the water contact behavior of their child. All questionnaires were verbally administered in the local language.

Written informed consent was obtained from the parent or guardian of each child before enrollment, and the children gave verbal assent for participation in the study. Study procedures were approved by the institutional review boards of the University of Georgia and the Centers for Disease Control and Prevention, the Scientific Steering Committee of the Kenya Medical Research Institute (KEMRI), and the KEMRI/National Ethics Review Committee of Kenya.

Immunological Testing

Antibody evaluation. A standardized enzyme-linked immunosorbent assay for soluble worm antigen preparation (SWAP)—specific IgE was performed on plasma from venous blood, as described elsewhere [24]. An external positive control (PC) comprised of a pooled sample of plasma from high-responding adults and a negative control of normal human serum (NHS) from volunteers from areas of nonendemicity was run on each

Table 1. Baseline Demographic Characteristics of Children in Study Arms A and B

Characteristic	Arm A (n = 68)	Arm B (n = 49)	P
<i>Schistosoma mansoni</i> egg count, geometric mean (95% CI), egg	94 (66–133)	79 (56–110)	.560
Male sex	55.9	57.1	.893
<i>Plasmodium falciparum</i> prevalence	28.1	21.4	.455
STH prevalence	57.4	40.4	.076
Any water contact ^a	94.9	95.7	.842
Frequent water contact ^b	84.8	89.4	.488

NOTE. Data are percentage of children, unless otherwise indicated. CI, confidence interval; egg, eggs per gram of feces; STH, soil-transmitted helminth.

^a Contact with lake at least once a month.

^b Contact with lake at least once a week.

plate. The optical density (OD) of the anti-SWAP IgE value for each sample was standardized according to the following formula: (sample – NHS)/(PC – NHS).

Whole blood phenotyping. Ethylenediaminetetraacetic acid–anticoagulated whole blood was analyzed by flow cytometry. Data acquisition and analysis were done on a dual-laser FACSCalibur flow cytometer with FlowJo software (version 7/8; Becton Dickinson). B cells were defined as cells that were positive for CD19. Gating to separate CD23⁺ B cells from CD23⁺ B cells was based on fluorescence minus one–stained samples, as reported elsewhere [12].

Statistical Analyses

The Wilcoxon rank sum test or the Kruskal-Wallis test was used for 2-sample or multiple-sample group comparisons, respectively. The Wilcoxon signed rank test was used for paired comparisons of the same children at different time points. All analyses were performed with Prism software (version 5; GraphPad) or SAS software (version 9.1; SAS Institute).

RESULTS

Baseline demographics. Baseline demographic characteristics of the study population are shown in Table 1. There were no significant differences between the 2 study arms in intensity of *S. mansoni* infection, sex, or coinfection with *P. falciparum* or STHs. Both groups had a similarly high frequency of self-reported water contact, with ~95% of children reporting contact with the lake at least once a month and >85% reporting weekly contact with the lake. In addition, there were no significant differences in any of these demographic factors between those children who did and those who did not complete the entire 2 years of follow-up.

***S. mansoni* infection over time.** The prevalence of *S. mansoni* infection at each follow-up time point in arm A is shown in Figure 1. Prevalence was reduced to 34% four months after

the initial praziquantel treatment. However, children became rapidly reinfected in this area of endemicity. Even with infected children receiving diagnoses and treatment at 4-month intervals, the prevalence of *S. mansoni* never decreased to <23% during the 2 years of follow-up.

Thirty-eight children (56%) in arm A had 2 or more positive diagnoses of *S. mansoni* infection after treatment for the *S. mansoni* infection present at baseline and before the end of the 2 years of follow-up. Nineteen children (28%) had 1 repeat diagnosis of *S. mansoni* infection during the course of follow-up, and 11 children (16%) went at least 2 years without becoming reinfected with *S. mansoni*, although 2 of these children were infected at the 2-year follow-up time point.

Geometric mean baseline egg counts in children with 0, 1, and ≥2 repeat diagnoses of *S. mansoni* infection were 54 (95% confidence interval [CI], 18–159), 64 (95% CI, 32–127), and 135 (95% CI, 87–209) eggs per gram of feces (epg), respectively. Although there was a trend toward higher initial intensity of infection in children with a greater number of repeat diagnoses of *S. mansoni* infection, the difference between the groups only approached statistical significance ($P = .059$). There were no differences in self-reported or parent-reported water contact between these groups.

Forty-three percent of the children in arm B were infected with *S. mansoni* at the 2-year follow-up time point, which approximated the overall baseline prevalence of 37% found in the initial survey of these schools. The mean intensity of infection among stool-positive children at the 2-year follow-up time point was 99 (standard deviation, 172) epg in arm A and 172 (standard deviation, 219) epg in arm B; the difference between arms was not significant ($P = .298$).

Changes in anti-SWAP IgE levels. Standardized anti-SWAP IgE levels at baseline and the 2-year follow-up time point in arms A and B are shown in Figure 2. Although anti-SWAP IgE levels slightly increased over the 2-year period, there were no statistically significant differences between baseline and 2-

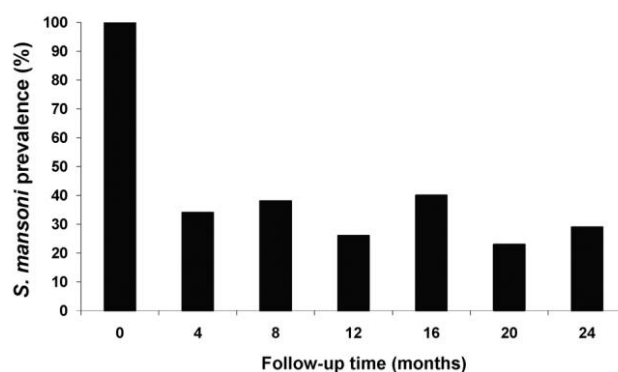


Figure 1. Prevalence of *Schistosoma mansoni* infection at each follow-up time point in study arm A.

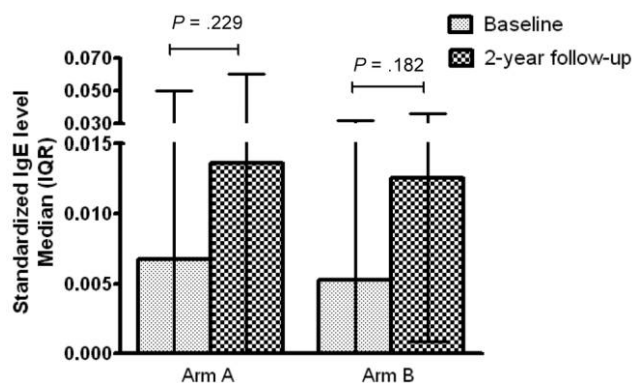


Figure 2. Anti-soluble worm antigen preparation immunoglobulin E (IgE) levels at baseline and the 2-year follow-up time point in study arms A and B. IQR, interquartile range.

year follow-up anti-SWAP IgE levels in either arm. There were also no statistically significant differences in baseline anti-SWAP IgE levels between arms A and B or in final anti-SWAP IgE levels between arms A and B.

Figure 3 depicts standardized anti-SWAP IgE levels at baseline and final follow-up for children in arm A, stratified by the number of repeat diagnoses of *S. mansoni* infection made during the 2 years of follow-up. Baseline anti-SWAP IgE levels in children with ≥ 2 repeat diagnoses were significantly lower than baseline levels in children who went at least 2 years without becoming reinfected. There was also a significant trend in decreasing baseline anti-SWAP IgE levels among children with 0, 1, and ≥ 2 repeat diagnoses of *S. mansoni* infection ($P = .002$). Children who had ≥ 2 repeat diagnoses (and who thus received a total of 3 or more treatments with praziquantel) over the 2 years of follow-up demonstrated significant increases in anti-SWAP IgE levels between baseline and the final 2-year follow-up time point. There were no significant changes in anti-SWAP IgE levels over time in those children who were not given a repeat diagnosis (and who thus received only the initial praziquantel treatment at baseline) or in those children who were given 1 repeat diagnosis (and who thus received a total of 2 praziquantel treatments) (Figure 3).

Changes in CD23⁺ B cell percentages. The mean percentage of CD23⁺ B cells in children in both study arms at baseline and the final follow-up time point is shown in Figure 4. The percentage of CD23⁺ B cells significantly increased between baseline and the 2-year follow-up time point in both arm A and arm B, but the difference in the CD23⁺ B cell percentage between the 2 arms at the 2-year follow-up time point was not statistically significant ($P = .076$).

When arm A was stratified by the number of repeat diagnoses of *S. mansoni* infection during follow-up (Figure 5), changes in CD23⁺ B cell percentages showed a pattern similar to that seen with anti-SWAP IgE levels. Although the difference did

not reach statistical significance ($P = .098$), children who were not reinfected before the 2-year follow-up time point had a higher percentage of CD23⁺ B cells at baseline than did children who had ≥ 2 repeat diagnoses of *S. mansoni* infection over the course of follow-up. The percentage of CD23⁺ B cells increased between baseline and the 2-year follow-up time point in children who had ≥ 2 repeat diagnoses of *S. mansoni* infection over the course of follow-up (and who thus received ≥ 3 praziquantel treatments) as well as in those children who had 1 repeat diagnosis (and who thus received 2 praziquantel treatments). However, the percentage of CD23⁺ B cells did not change significantly in those children who were not reinfected before the final follow-up (and who thus received only the initial praziquantel treatment).

Coinfection with *P. falciparum* and STHs. There was no difference in baseline anti-SWAP IgE levels between children coinfecting with *S. mansoni* and *P. falciparum* and children without *P. falciparum* infection (standardized OD value, 0.058 vs 0.055; $P = .282$) or between children coinfecting with *S. mansoni* and STHs and children without STH infection (standardized OD value, 0.062 vs 0.046; $P = .943$). There was also no difference in CD23⁺ B cell percentage between children coinfecting with *S. mansoni* and *P. falciparum* and children without *P. falciparum* infection (49.3% vs 46.9%; $P = .533$). There was a higher percentage of CD23⁺ B cells in children coinfecting with *S. mansoni* and STHs than in children without STH infection (57.8% vs 41.5%; $P = 0.018$). However, the difference in CD23⁺ B cell percentage in children infected with STHs and those not infected with STHs did not persist at the first follow-up time point (4 months) after treatment with albendazole and/or praziquantel (50.8% in STH-infected children and 51.6% in

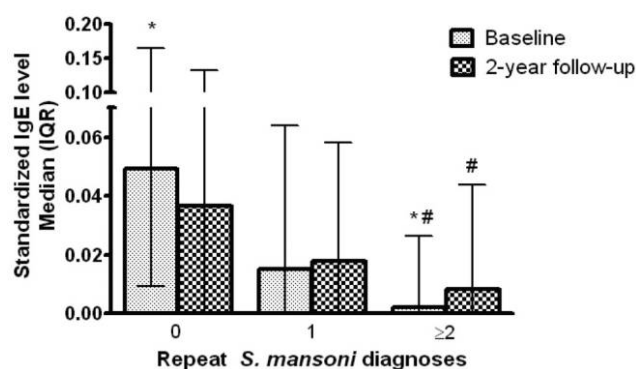


Figure 3. Anti-soluble worm antigen preparation (SWAP) immunoglobulin E (IgE) levels at baseline and the 2-year follow-up time point in study arm A, stratified by the number of praziquantel treatments received during the 2-year follow-up period. IQR, interquartile range. * $P < .05$ for the difference in baseline anti-SWAP IgE level between the 0 and ≥ 2 diagnoses groups (Wilcoxon paired test); *# $P < .05$ for the difference between baseline and the 2-year follow-up time point (Wilcoxon paired test).

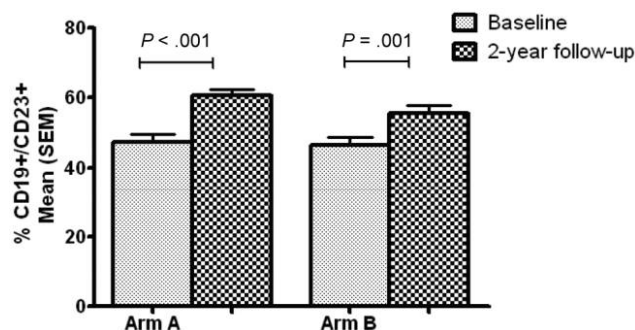


Figure 4. Percentage of CD19⁺CD23⁺ cells at baseline and the 2-year follow-up time point in study arms A and B. SEM, standard error of the mean.

STH-uninfected children). This was true regardless of *S. mansoni* infection status at 4 months (data not shown). At no other time point throughout the course of follow-up did children infected with STHs have a higher percentage of CD23⁺ B cells than children not infected with STHs.

DISCUSSION

Our data suggest high *S. mansoni* transmission in this area along Lake Victoria in western Kenya. After 2 years of diagnosing and treating infected children every 4 months, the prevalence of *S. mansoni* in arm A of our cohort was still ~30%. This is close to the overall prevalence of 37% found in our initial survey of 8–10-year-old children in the study area. More than half (56%) of the children in arm A had 2 or more positive diagnoses of *S. mansoni* infection during the 2 years after treatment of the initial infection. Because we did not assess cure after each treatment, we cannot be certain that each positive diagnosis represented a reinfection rather than a cure failure. However, given that the cure rate of praziquantel is >70% after 1 dose [25, 26], the majority of these positive diagnoses likely represented true cures and reinfections.

The original design of the study was to examine differences in immune parameters between children kept as free of *S. mansoni* infection as possible for 2 years (arm A) and children treated only once 2 years prior (arm B). When arm A was analyzed as a group, however, we did not find a difference in levels of schistosome-specific IgE between arms A and B at the end of the study. What we did not anticipate was that some children in this area had developed an apparent level of resistance to reinfection before age 8–10 years (when they were enrolled in this study), as they did not become reinfected for 2 years after 1 praziquantel treatment. When arm A was stratified according to the number of diagnoses of *S. mansoni* infection each child had during follow-up, which is a close approximation of how many times the child was reinfected, those children who did not become reinfected for at least 2 years

after treatment of their baseline infection had significantly higher levels of anti-SWAP IgE and borderline significantly higher levels of CD23⁺ B cells than did the more susceptible children who had at least 2 repeat diagnoses of *S. mansoni* infection (and likely ≥ 2 reinfections) within 2 years. After 3 or more praziquantel treatments, both anti-SWAP IgE and the percentage of CD23⁺ B cells had significantly increased in the more susceptible children, indicating that frequent treatment of infected children can drive immune responses to more closely resemble those of the children who remained uninfected over the course of follow-up.

Numerous studies have reported an association between higher levels of schistosome-specific IgE and resistance to reinfection with *S. mansoni* [8–11]. We recently reported increases in anti-SWAP IgE levels that paralleled the change from a state of susceptibility to *S. mansoni* infection to a state of increased resistance to reinfection in our cohort of male adults undergoing repeated cycles of treatment and reinfection [27]. We also recently reported a correlation between CD23⁺ B cell percentage and level of resistance to *S. mansoni* reinfection in our cohort of male adults, suggesting that B cells expressing CD23 may play a role in the development of protective immunity [12]. CD23 is the low-affinity receptor for IgE and has been shown to be essential for IgE-mediated enhancement of specific immune responses in murine models [28].

We did not observe an increase in anti-SWAP IgE levels in children who received 2 praziquantel treatments over the course of follow-up. However, this group was likely composed of children who experienced cure failure after the initial praziquantel treatment, children who had already developed an intermediate level of resistance, and children who had >1 reinfection but whose reinfections were not diagnosed as repeat positive results because of the insensitivity of the Kato-Katz test on a single stool sample. Although there was an overall increase in the percentage of CD23⁺ B cells during the 2-year period in both

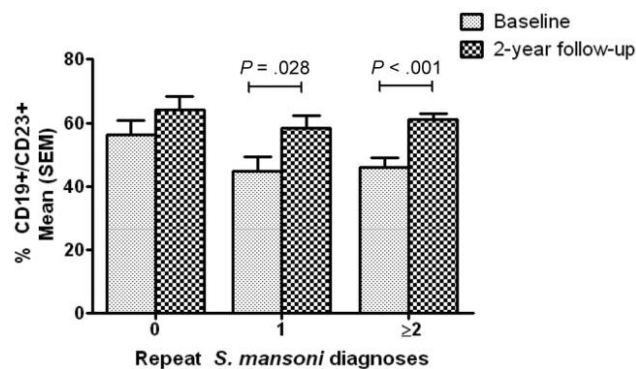


Figure 5. Percentage of CD19⁺CD23⁺ cells at baseline and the 2-year follow-up time point in study arm A, stratified by the number of praziquantel treatments received during the 2-year follow-up period. SEM, standard error of the mean.

study arms, this was not unexpected given that studies have shown that the proportion of B lymphocytes expressing CD23 slowly increase until age 12 in healthy pediatric populations [29, 30]. However, within arm A the increase was more dramatic among the more susceptible children who received ≥ 3 praziquantel treatments than among the more resistant children who required only 1 initial praziquantel treatment.

A high level of coinfection with *S. mansoni*, *P. falciparum*, and STHs was present in this population. We found no association between levels of schistosome-specific IgE and coinfection with either *P. falciparum* or STHs. Children coinfecting with STHs and *S. mansoni* at baseline had a statistically significantly higher percentage of CD23⁺ B cells than did children without STH infection. A higher percentage of CD23⁺ B cells in coinfecting children was seen only at baseline, when they likely had long-term *S. mansoni* and STH infections. The difference did not persist after treatment of their infections at baseline.

In conclusion, we found that some children in this area of high endemicity exhibited a phenotype indicative of resistance to *S. mansoni* reinfection by 8–10 years of age. Infections in lakeside communities have been shown to begin very early in life [31], and some of our 8–10-year-old subjects could have been infected for 7–9 years at the time of their enrollment, providing an opportunity for them to have already experienced dying worms. The resistant phenotype was characterized by high schistosome-specific IgE levels and elevated levels of CD23⁺ B cells. Frequent praziquantel treatment of more susceptible children increased these immune responses toward protective levels. The effect of praziquantel treatment on the production of anti-SWAP IgE and CD23⁺ B cells was obscured when data were analyzed without accounting for differences in prior development of apparent resistance to *S. mansoni*.

References

- Kabaterine NB, Vennervald BJ, Ouma JH, et al. Adult resistance to schistosomiasis mansoni: age-dependence of reinfection remains constant in communities with diverse exposure patterns. *Parasitology* **1999**; 118:101–105.
- King CH, Keating CE, Muruka JE, et al. Urinary tract morbidity in schistosomiasis haematobia: associations with age and intensity of infection in an endemic area of Coast Province, Kenya. *Am J Trop Med Hyg* **1988**; 39:361–368.
- Wilkins HA, Goll PH, Marshall TFD, Moore PJ. Dynamics of *Schistosoma haematobium* infection in a Gambian community. III. Acquisition and loss of infection. *Trans R Soc Trop Med Hyg* **1984**; 78:227–232.
- Fulford AJ, Butterworth AE, Ouma JH, Sturrock RF. A statistical approach to schistosome population dynamics and estimation of the life span of *Schistosoma mansoni* in man. *Parasitology* **1995**; 110(Pt 3):307–316.
- Warren KS, Mahmoud AAF, Cumming P, Murphy DJ, Houser HB. Schistosomiasis mansoni in Yemen in California: duration of infection, presence of disease, therapeutic management. *Am J Trop Med Hyg* **1974**; 23:902–909.
- Woolhouse MEJ, Hagan P. Seeking the ghost of worms past. *Nature Med* **1999**; 5:1225–1227.
- Karanja DMS, Hightower AW, Colley DG, et al. Resistance to reinfection with *Schistosoma mansoni* in occupationally exposed adults and effect of HIV-1 co-infection on susceptibility to schistosomiasis: a longitudinal study. *Lancet* **2002**; 360:592–596.
- Dunne DW, Butterworth AE, Fulford AJC, et al. Immunity after treatment of human schistosomiasis: association between IgE antibodies to adult worm antigens and resistance to reinfection. *Eur J Immunol* **1992**; 22:1483–1494.
- Caldas IR, Correa-Oliveira R, Colosimo E, et al. Susceptibility and resistance to *Schistosoma mansoni* reinfection: parallel cellular and isotypic immunologic assessment. *Am J Trop Med Hyg* **2000**; 62:57–64.
- Webster M, Fallon PG, Fulford AJC, et al. Effect of praziquantel and oxamniquine treatment on human isotype responses to *Schistosoma mansoni*: elevated IgE to adult worm. *Parasite Immunol* **1997**; 19:333–335.
- Zhaosong Z, Haiwei W, Suchen C, et al. Association between IgE antibody against soluble egg antigen and resistance to reinfection with *Schistosoma japonicum*. *Trans R Soc Trop Med Hyg* **1997**; 91:606–608.
- Mwinzi PNM, Ganley-Leal L, Black CL, Secor WE, Karanja DMS, Colley DG. Circulating CD23⁺ B cell subset correlates with the development of resistance to *Schistosoma mansoni* reinfection in occupationally exposed adults who have undergone multiple treatments. *J Infect Dis* **2009**; 199:272–279.
- Suryani S, Fulcher DA, Santner-Nanan B, et al. Differential expression of CD21 identifies developmentally and functionally distinct subsets of human transitional B cells. *Blood* **2010**; 115:519–529.
- McClosky N, Hunt J, Beavil RL, et al. Soluble CD23 monomers inhibit and oligomers stimulate IgE synthesis in human B cells. *J Biol Chem* **2007**; 282:24083–24091.
- Aubry JB, Pochon S, Graber P, Jansen KU, Bonnefoy JY. CD21 is a ligand for CD23 and regulates IgE production. *Nature* **1992**; 358:505–507.
- Su TT, Guo B, Wei B, Braun J, Rawlings DJ. Signaling in transitional type 2 B cells is critical for peripheral B-cell development. *Immunol Rev* **2004**; 197:161–178.
- Hjelm F, Karlsson MC, Heyman B. A novel B cell-mediated transport of IgE-immune complexes to the follicle of the spleen. *J Immunol* **2008**; 180:6604–6610.
- Rambert J, Mamani-Matsuda M, Moynet D, et al. Molecular blocking of CD23 supports its role in the pathogenesis of arthritis. *PLoS One* **2009**; 4:e4834.
- Stief A, Texido G, Sansig G, Eibel H, Le Gros G, van der Putten H. Mice deficient in CD23 reveal its modulatory role in IgE production but no role in T and B cell development. *J Immunol* **1994**; 152:3378–3390.
- Mutapi F, Ndhlovu PD, Hagan P, Woolhouse MEJ. A comparison of humoral responses to *Schistosoma haematobium* in areas with low and high levels of infection. *Parasite Immunol* **1997**; 19:255–263.
- Mutapi F, Ndhlovu PD, Hagan P, et al. Chemotherapy accelerates the development of acquired immune responses to *Schistosoma haematobium* infection. *J Infect Dis* **1998**; 178:289–293.
- Mutapi F, Hagan P, Woolhouse MEJ, Mduluzi T, Ndhlovu PD. Chemotherapy-induced, age-related changes in antischistosome antibody responses. *Parasite Immunol* **2003**; 25:87–97.
- Handzel T, Karanja DMS, Addiss DG, et al. Geographic distribution of schistosomiasis and soil-transmitted helminthes in western Kenya: implications for antihelminthic treatment. *Am J Trop Med Hyg* **2003**; 69:318–323.
- Ganley-Leal LM, Mwinzi PN, Cetre-Sossah CB, et al. Correlation between eosinophils and protection against reinfection with *Schistosoma mansoni* and the effect of human immunodeficiency virus type 1 coinfection in humans. *Infect Immun* **2006**; 74:2169–2176.
- Gryseels B, Nkuliya L, Coosemans MH. Field trials of praziquantel and oxamniquine for the treatment of schistosomiasis mansoni in Burundi. *Trans R Soc Trop Med Hyg* **1987**; 81:641–644.

26. World Health Organization. The control of schistosomiasis. WHO Technical Report Series **1993**; 1–86.
27. Black CL, Mwinzi PNM, Muok EMO, et al. Influence of exposure history on the immunology and development of resistance to human schistosomiasis mansoni. PLoS Negl Trop Dis **2010**; 4(3):e637.
28. Fujiwara H, Kikutani H, Suematsu S, et al. The absence of IgE antibody-mediated augmentation of immune responses in CD23-deficient mice. Proc Natl Acad Sci U S A **1994**; 91:6835–6839.
29. Veneri D, Ortolani R, Franchini M, Tridente G, Pizzolo G, Vella A. Expression of CD27 and CD23 on peripheral blood B lymphocytes in humans of different ages. Blood Transfus **2009**; 7:29–34.
30. Erkeller-Yuksel FM, Deneys V, Yuksel B, et al. Age-related changes in human blood lymphocyte populations. J Pediatr **1992**; 120:216–222.
31. Odogwu SE, Ramamurthy NK, Kabatereine NB, et al. *Schistosoma mansoni* in infants (aged <3 years) along the Ugandan shoreline of Lake Victoria. Ann Trop Med Parasitol **2006**; 100:315–326.