Am. J. Trop. Med. Hyg., 83(3), 2010, pp. 534-541
doi:10.4269/ajtmh.2010.10-0033;

Effects of Annual Mass Treatment with Ivermectin for Onchocerciasis on the Prevalence of Intestinal Helminths

Julie Gutman*

INTRODUCTION

The soil transmitted helminths (STH), primarily *Ascaris lumbricoides*, hookworms (*Necator americanus*, and *Ancyclostoma duodenale*), and *Trichuris trichiura*, are highly prevalent in Nigeria, as in most of sub-Saharan Africa.[1-4] They are responsible for significant morbidity and mortality worldwide, causing an estimated loss of 39 million disability adjusted life years (DALYs).[5] This disability burden is greater than that due to malaria (35.7 million DALYs),[5] yet in comparison, STH are among the most neglected of the "neglected tropical diseases." The STH infections disproportionately affect those living in the most resource poor settings, where the infections' effects contribute to the continued cycle of poverty. Although the ultimate goal involves elimination of STH infections through improved hygiene and sanitation, achieving this goal will take time and considerable resources. In the meantime, reductions in morbidity and mortality can be achieved through mass treatment programs, similar to those in place for onchocerciasis and lymphatic filariasis.[6, 7] Treatment of intestinal helminths has been shown to have beneficial effects on growth and nutrition, child mortality, and school performance.[8-10]

The most recently published World Health Organization (WHO) guidelines (2006) recommend treatment of all school-aged children (SAC) twice a year in communities where the prevalence of infection exceeds 50% in a sample of SAC, and once a year if the prevalence is 20–50%.[11] With a prevalence of less than 20%, treatment on a case by case basis is recommended.[11] The guidelines also recommend treatment of preschool-aged children (PAC) but do not give guidance on how often. The Global Target put forth by the World Health Assembly Resolution 54.19 in 2001 is that at least 75% of all school-aged children at risk of morbidity from schistosomiasis and STH should be regularly reached and treated by the year 2010. As we have reached this deadline, it is imperative to look at how current programs aimed at other tropical diseases, such as onchocerciasis, may be helping to meet this goal.

Ivermectin (IV) causes paralysis and death of many nematode parasites.[12] It is the drug of choice for onchocerciasis and is routinely used as a mass treatment agent in onchocerciasis and lymphatic filariasis treatment programs, supplied by a generous donation from Merck & Co. Ivermectin was included in the list of WHO recommended drugs[11] for treatment of STH (except hookworms) in 2002, but has since been replaced on the list by the benzimidazole class of anthelmintics.[13] A few studies in humans have shown ivermectin to be efficacious against *Ascaris* (cure rates 78.4–100%)[14-17] and *Strongyloides* (cure rates 83–84%),[15, 18] but have had mixed results for the treatment of *Trichuris* (cure rates 11%, 35.2%, 85%)[14, 15, 17, 19]

twice per year IV therapy in northeastern Ecuador on STH. However, no studies have been done to look at the effect on the prevalence of STH following annual mass drug administration (MDA) with IV for onchocerciasis that occurs at approximately 40 million treatments per year in Africa. [24]

The use of annual IV distribution to prevent morbidity caused by onchocerciasis began in Imo state, Nigeria, in 1993 and reached statewide in 1995 following a national onchocereciasis assessment survey that showed high prevalence of onchocerciasis throughout much of southeastern Nigeria. [6, 25] This program was begun as a combined effort of the State Ministry of Health, the Lions Clubs, and the River Blindness Foundation. For a time it also received support from the African Program for Onchocerciasis Control (APOC). The distribution program is now run by the State Ministry of Health in conjunction with The Carter Center. Imo State is composed of 27 districts known as local government areas (LGAs). On the basis of the 1995 disease mapping for onchocerciasis, 18 of the 27 LGAs in Imo state receive annual IV therapy because onchocerciasis is a public health problem there. In affected villages,

bacreas (un br buse the

METHODS

Sampling methodology. From July to August, 2008, we performed a cross-sectional survey of STH prevalence in Imo state, Nigeria. We used a stratified sampling procedure to choose 40 villages, 20 treated and 20 untreated villages (

his/her name recorded. The child or child's guardian was instructed to put a walnut sized amount of feces (size showed with a rock) of his or her stool from the next morning into the collection cup using a wooden stick, which was provided. The child/guardian was also instructed to wash his/her hands

skewed toward low egg counts. For this reason, logarithmic transformation and geometric means were calculated for fecal egg density using antilog-1 where x = number of

untreated area ($P = 0.07$). Only light intensity *Trichuris* infections were seen in the treated areas, whereas 3 children (5.7%) had moderate intensity infections in the untreated area ($P = 0.55$). Heavy infections with hookworm occurred in 3.2% and 1.8% of children in the treated and untreated area, and moderate intensity infections occurred in 2.1% and 2.7% of children in the treated and untreated area ($P = 0.77$). Only one child was found to be infected with *S. mansoni*, none were infected with *Schistosoma hematobium.*

Preschool-aged. Among preschool-aged children, who had never received IV even in treated areas, there was a significant difference in the prevalence of infection with *Trichuris* in the treated (1%) compared with untreated areas (8%) ($P = 0.019$). The difference in the prevalence of *Ascaris* infection approached statistical significance (3% versus 10%, $P = 0.051$). There was no difference in the prevalence of hookworm infection (21% versus 27%, $P = 0.30$). Geometric mean egg counts per gram of stool among all children 2 ±4 years of age were higher in untreated versus treated MDA; this difference was significant for *Ascaris* and *Trichuris* but not for hookworm (*Ascaris*: 0.91 [95% CI 0.30 ±1.83] versus 0.24 [95% CI 0 ±0.59], $P = 0.04$; *Trichuris*: 0.39 [95% CI 0.12 ±0.73] versus 0.05 [95% CI 0 ±0.14], $P = 0.01$; hookworm: 2.44 [95% CI 1.30 ±4.14] versus 1.74 [95% CI 0.82 ±3.12], $P = 0.36$). The range of eggs per gram of stool in untreated versus treated areas was 0 ±18,648 for *Ascaris*, compared with 0 ±6,000 in the treated region, 0 ±312 versus 0 ±96 for *Trichuris*, and 0 ±624 versus 0 ±1,632 for hookworm. Three children had *Ascaris* infection of moderate intensity; one in the treated and two in the untreated areas, respectively ($P = 1$). The infections with *Trichuris* and hookworm were all of light intensity. There was one case of infection with *S. mansoni.*

Effects of ivermectin on the need for community treatment. From a community perspective, nearly all the villages required at least school-based therapy for hookworm; six of the untreatedBT1 0 0 1 370.63 349.97 Tm[(ba)4(se)7

six3JET EMC /P <</MCID 2>> 6DC BT/F4 0 1 385.130598.22 51[(six)The5(sa)4(. TJETBT/F3 0 1 194.3 501.22 51[(six))-

View larger version (23K):
[in a new window]

FIGURE 2.

View this table:
[in a new window]

TABLE 3
Univariate and multivariate analysis of factors contributing to infection among SACs

untreated groups. Although we found a significant impact of ivermetin on the prevalence of *Ascaris* and *Trichuris*, there was no difference in the prevalence or intensity of infection with hookworm in the treated versus untreated areas. The lack of efficacy against hookworm, the STH most associated with causing anemia and intestinal inflammation, explains the lack of difference in growth parameters.

The current WHO guidelines advocate STH treatment of PACs, but provide no specific recommendations as to how often this treatment should be given. In addition, treatment of PACs is not addressed in the World Health Assembly Resolution. Although school-aged children typically have a higher worm burden than preschool-aged children, PACs are still at risk for infection, as shown in our study and others. [3, 34-36] Very few studies have been done looking at the negative effects on growth and development in the PAC age group. However, given the rapid rate of development it is conceivable that infections in this age may be more deleterious to subsequent growth and cognitive development than infections suffered in later childhood. The available data shows that deworming of STH-infected PAC improves their health and allows them to reach their cognitive potential. [34, 37] Although treatment of SAC may decrease the prevalence in the rest of the community, including in PAC, treatment in this age still appears warranted if age appropriate antihelminthic preparations can be manufactured.

Although intermittent chemotherapy provides a useful tool to combat STH infections, long-term control and eradication of STH infections will require significant improvements in hygiene and sanitation. Reporting consistent latrine use was associated with a decreased rate of infection with both hookworm and *Trichuris*, although not with *Ascaris*. This is in keeping with a study by Sorensen and others, [38] which also found that latrine ownership had more impact on hookworm infection than on *Trichuris* or *Ascaris*. Nguyen and others[39] also found that hookworm infection, but not *Ascaris* or *Trichuris*, was associated with lack of a closed latrine (OR = 2.0). Other studies have found improved sanitation alone to be an insufficient control measure for intestinal helminth infections, but have not noted a differential effect with different intestinal parasites. [40, 41]

Reported use of shoes was not associated with a lower prevalence of hookworm infection; although this has previously been reported to be protective against hookworm infection. [42] However, so few children reported shoe use that this finding is probably not noteworthy. In addition, those wearing shoes used "flip-flops," which do not provide much protection from soil, especially in the rainy season.

A history of passing worms was associated with an increased risk of infection, both overall and for each specific type of infection. However, it was neither a sensitive nor specific marker of infection. This suggests that questioning children regarding passing of worms should not be used in place of stool examinations to determine whether villages are in need of treatment of STH.

A weakness of this study was that the baseline level of STH infection in these villages was not obtained before initiating MDA. Although the villages sampled were matched as closely as

infection, we cannot be sure that the treated villages had the same initial prevalence and intensity of STH as the untreated villages. However, given the similar hookworm findings between areas, and the known properties of ivermectin against the STHs, we think our assumption that *Ascaris* and *Trichuris* levels were similar before IV interventions began is reasonable.

Further studies are indicated to determine if annual IV and albendazole will suffice to control STHs in IV-treated onchocerciasis areas where STH prevalence is > 50%, so averting the need to invest in an additional treatment round. In addition, preschool-aged children are at risk for STH infections and better studies and age appropriate drug preparations are needed to guide recommendations for STH treatment in this age group.

Received January 18, 2010. Accepted for publication May 5, 2010.

ACKNOWLEDGMENTS

We thank Josephine Obiezu who entered the data; Stanley Asiawuchi, Afam Okonkwo, and Francis Ugwu who prepared and read all the slides; Jon Nnachi and Aaron Iroaja who assisted in data collection; Aryc Mosher for preparing the map in Figure 1; all the community health workers, villagers, and children who participated; and Daniel Newman for proofreading and allowing his wife (Julie Gutman) to leave him for a month of field work.

Financial support: We gratefully acknowledge the Izumi Foundation and the Bill and Melinda Gates Foundation for their generous funding. Julie Gutman's salary was supported in part by PHS Grant UL1 RR025008 and KL2 RR025009 from the Clinical and Translational Science Award program, national Institutes of Health, National Center for Research Resources and a fellowship grant from the Pediatric Infectious Disease Society [PIDS].

Authors' addresses: Julie Gutman, Emory University School of Medicine, Department of Pediatric Infectious Disease, E-mail: gutmanjr@gmail.com. Emmanuel Emukah, Njideka Okpala, and Andrew Obasi, The Carter Center Southeast Programs, Nigeria, E-mails: emukahe@yahoo.com, talk2nj2003@yahoo.com, and andyobasi2@yahoo.com Chinyere Okoro, Parasitology Unit, Microbiology Department, Federal Medical Center, Owerri, Imo State, Nigeria, E-mail: ihuarulam2002@yahoo.com. Emmanuel S. Miri, The Carter Center Nigeria, Jos, Nigeria, E-mail: emmamiri@yahoo.com. Frank O. Richards, Jr., The Carter Center, Atlanta, GA, E-mail: frich01@emory.edu

*Address correspondence to Julie Gutman, Department of Pediatric Infectious Disease, Emory University School of Medicine, 2015 Uppergate Dr. NE, Atlanta, GA 30322. E-mail: gutmanjr@gmail.com

REFERENCES

1. Kirwan P, Asaolu S, Molloy S, Abiona T, Jackson A, Holland C, 2009. Patterns of soil-transmitted helminth infection and impact of four-monthly albendazole treatments in preschool children from semi-urban communities in Nigeria: a double-blind placebo-controlled randomised trial. *BMC Infect Dis 9*: 20.[CrossRef][Medline]

2. Chan M, 1997. The global burden of intestinal nematode infections ² fifty years on. *Parasitol Today 13*: 438 ±443.[CrossRef][Web of Science][Medline]

3. Kirwan P, Asaolu SO, Abiona TC, Jackson AL, Smith HV, Holland CV, 2009. Soil-transmitted helminth infections in Nigerian children aged 0 ±25 months. *J Helminthol 83*: 261 ±266.[CrossRef][Web of Science][Medline]

4. Uneke C, Eze KO, Oyibo PG, Azu NC, Ali E, 2007. *Soil-Transmitted Helminth Infection In School Children In South-Eastern Nigeria: The Public Health Implication*. The Internet Journal of Third World Medicine. *Volume 4*.

5. World Health Organization, 2002. *Prevention and Control of Schistosomiasis and Soil Transmitted Helminths: report of a WHO expert committee*. World Health Organization Technical Report Series 912.

6. Hopkins D, Eigege S, Miri ES, Gontor I, Ogah G, Umaru J, Gwomkudu CD, Matha W, Jinadu MY, Amadiegwu S, Oyeneka OK, Korve K, Richards F, 2002. Lymphatic filariasis elimination and schistosomiasis control in combination with onchocerciasis control in Nigeria. Am J Trop Med Hyg 67: 266 ±272.[Abstract]

7. Emukah E, Oshuoha E, Miri ES, Onyenama J, Amazigo U, Obijuru C, Osuji N, Ekeanyanwu J, Amadiegwu S, Korve K, Richards FO, 2004. A longitudinal study of impact of repeated mass ivermectin treatment on clinical manifestations of onchocerciasis in Imo State, Nigeria. Am J Trop Med Hyg 70: 556 ± 561.[Abstract/Free Full Text]

8. Bleakley H, 2003. Diseases and development: evidence from the American South. *J Eur Econ Assoc 1*: 376 ±386.[CrossRef]

9. Stephenson L, Latham MC, Ottesen EA, 2000. Malnutrition and parasitic helminth infections. *Parasitology 121*: S23 ±S28.[CrossRef][Web of Science][Medline]

severely affected population. *Bull World Health Organ 82*: 563–571.[Web of Science][Medline]

21. Taticheff S, Kebede A, Bulto T, Werkeneh W, Tilahun D, 1994. Effect of ivermectin (Mectizan) on intestinal nematodes. Ethiop Med J 32: 7–15.[Web of Science][Medline]

22.

31. Oberhelman RA, Guerrero ES, Fernandez ML, Silio M, Mercado D, Comiskey N, Ihenacho G, Mera R, 1998. Correlations between intestinal parasitosis, physical growth, and psychomotor development among infants and children from rural Nicaragua. Am J Trop Med Hyg 58: 470 ±475.[Abstract]

32. Moore SR, Lima AA, Conaway MR, Schorling JB, Soares AM, Guerrant RL, 2001. Early childhood diarrhoea and helminthiases associate with long-term linear growth faltering. Int J Epidemiol 30: 1457 ±1464.[Abstract/Free Full Text]

33.

Hoa Binh province, Vietnam. *Trans R* Soc Trop Med Hyg 103: 237 ± 241.[CrossRef][Web of Science][Medline]

41. Asaolu S, Ofoezie IE, Odumuviwa PA, Sowemimo OA, Ogunniyi TA, 2002. Effect of water supply and sanitation on the prevalence and intensity of *Ascaris lumbricoides* among pre-school-age children in Ajebandele and Ifewara, Osun State, Nigeria. Trans R Soc Trop Med Hyg 96: 600 ± 604.[CrossRef][Web of Science][Medline]

42. Chongsuvivatwong V, Pas-Ong S, McNeil D, Geater A, Duerawee M, 1996. Predictors for the risk of hookworm infection: experience from endemic villages in southern Thailand. *Trans R Soc Trop Med Hyg 90*: 630 ± 633.[CrossRef][Web of Science][Medline]