Evaluation of the Impact of Overseas Pre-departure Treatment for Infection with Intestinal Parasites among Montagnard Refugees Migrating from Cambodia to North Carolina

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Abstract. We evaluated the effectiveness of an overseas pre-departure regimen of five days of albendazole for presumptive treatment of intestinal parasites by examining stool specimens in treated and untreated Montagnard refugees after arrival in the United States. Among 815 refugees evaluated, fully treated refugees had a significantly lower prevalence of helminths (11 [1.4%] of 777), specifically hookworm and Ascaris lumbricoides, than untreated pregnant women (3 [20%] of 15) (P < 0.001). Multivariate analysis showed that treatment was associated with significantly lower rates of infection with helminths but not protozoa. Post-arrival gastrointestinal symptoms were not associated with findings on stool examination. Our evaluation suggests that although additional studies are needed to determine optimal treatment regimens for intestinal parasites, especially among young children and pregnant women, a five-day course of pre-departure albendazole was effective in reducing helminthic infection in treated refugees.

INTRODUCTION

The World Health Organization reports a high global burden of intestinal parasitic disease, which affects more than two billion people per year.1 Previous studies of refugee populations from Africa and Asia resettling in the United States have demonstrated substantial burdens of intestinal parasitic infection.2–8 Among 402 Vietnamese Montagnard refugees screened after resettlement in North Carolina in 1992, virtually all were infected with at least one intestinal parasite.7 In 1997, the U.S. Centers for Disease Control and Prevention (CDC) piloted an enhanced refugee health program for Barawan Somali refugees in Kenya, which included pre-departure treatment of intestinal parasites.4 Since 1998, it has been standard practice for refugees from Africa, and since 1999, for refugees from Southeast Asia, to receive pre-departure treatment with one 400-mg dose of albendazole as presumptive treatment for intestinal parasites. Later studies of the impact of this overseas pre-departure treatment regimen demonstrated low rates of infection with intestinal helminths and some protozoa among African and Southeast Asian refugees resettling in Massachusetts and Minnesota.2,9

In 2001, land rights disputes caused more than 1,000 Montagnards to flee the central highlands of Vietnam. After a period of time in which they likely did not have access to clean water and adequate sanitation in the forests of Vietnam, they were sheltered for almost a year in temporary camps administered by the United Nations High Commissioner for Refugees in two northeastern Cambodian provinces. Refugees lived in family housing units and had pit latrines, water from streams or wells with charcoal for boiling it, and access to medical services. In April 2002, they were relocated from the camps to an abandoned factory in Phnom Penh, Cambodia, where they had access to running water and a latrine in a public area. There, they were screened in preparation for urgent resettlement in North Carolina.

As part of the resettlement process, CDC, the International Organization for Migration (IOM), and the North Carolina Division of Public Health tailored an enhanced refugee health program to meet this population’s needs. Malaria-related screening and treatment have been previously described.10 Pre-departure interventions for intestinal parasitosis included administering a five-day course of albendazole for presumptive treatment of intestinal parasitosis. A five-day course was chosen instead of one dose because a recent analysis demonstrated the cost-effectiveness of the longer regimen for treating immigrants from countries endemic for strongyloidiasis and other common intestinal helminthic infections.5 We considered treatment for infection with Strongyloides stercoralis especially important because of its ability to infect its host for decades and the threat of hyperinfection and disseminated infection in persons who become immunocompromised.

To assess the impact of the five-day pre-departure treatment regimen, we conducted medical assessments and examined stool samples for parasites shortly after the refugees arrived in the United States.

MATERIALS AND METHODS

Evaluation and treatment. From April 29 to May 24, 2002, IOM and CDC screened and treated the Montagnard refugees before their departure from Phnom Penh. Except for pregnant women and children less than two years of age, who were excluded from treatment, all refugees received 400 mg of albendazole for five days under direct observation. Demographic, clinical, and treatment information was recorded by using standard forms and entered into a Microsoft (Redmond, WA) Access database. Informed consent was obtained from participants, and the evaluation was conducted in compliance with federal regulations governing the protection of human subjects.

From June 2002 through April 2003, clinical and laboratory assessments were conducted at five North Carolina county

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health departments on all refugees within 90 days of their arrival in the United States. Gastrointestinal symptoms, including abdominal pain, nausea, vomiting, diarrhea, bloody stools, and weight loss, were ascertained. Instructions for stool collection were also provided on video, orally in tribal languages, and in written Vietnamese. All refugees were asked to collect one stool specimen every other day for three days in 10% formalin-filled vials. Those persons with gastrointestinal symptoms were also asked to submit three additional specimens in containers filled with low-viscosity polyvinylacrylate (LV-PVA).12 At a second visit, persons with parasitic infections received appropriate treatment.13

**Laboratory evaluation.** The North Carolina State Laboratory for Public Health (NCSLPH) examined all specimens. To increase sensitivity for detecting *Giardia intestinalis* and other parasites, up to three specimens per refugee were pooled.14 An aliquot of the pooled formalin-fixed specimens from each person was concentrated by the formalin ethylacetate concentration method, and wet mounts were examined microscopically (22 × 22 mm² cover slip area) at 10×, 20×, and/or 40× magnification. Pooled specimens collected in LV-PVA were stained with Wheatley’s trichrome and examined under oil immersion (100×).15 Parasites were identified by species and classified as pathogenic protozoa (*G. intestinalis*, nonpathogenic protozoa, or helminths (all pathogenic). *Entamoeba histolytica* and *E. dispar* were not differentiated and were classified as potentially pathogenic, and *Blastocystis hominis* was considered nonpathogenic.

The Division of Parasitic Diseases, CDC (Atlanta, GA) performed quality assurance on specimens collected from June 1, 2002, through August 31, 2002. Aliquots of all concentrated samples with positive findings and 10% of those with negative findings were collected in Sarstedt (Nümbrecht, Germany) tubes. They were processed and examined by the same methods used by the NCSLPH.

**Data analysis.** Results of the microscopic stool examinations were analyzed to compare differences between treated and untreated groups of refugees and to examine other potential risk factors for parasitic infection, such as age and sex. A logistic regression model, controlling for age and sex, was used to assess the impact of albendazole treatment on infection with intestinal parasites. A P value < 0.05 was considered statistically significant for the purpose of inference to a larger population of similar refugees.

Information on post-resettlement symptoms was recorded for the 491 refugees who were seen in North Carolina clinics during June–September 2002. The sensitivity and specificity of clinical symptoms for infection with intestinal parasites were calculated by using the NCSLPH stool examination as the reference for presence of infection.

For the laboratory quality assurance analysis, results from the NCSLPH and CDC laboratory evaluation of pooled specimen sets were compared. The CDC findings were used as reference to calculate sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV). The results of laboratory examination of stool specimens fixed in LV-PVA were also compared for concordance with corresponding specimens fixed in formalin. Data were analyzed by using version 8.0 of the SAS system for Windows (SAS Institute Inc., Cary, NC).

**RESULTS**

**Overseas treatment status and demographics of Montagnard refugees, North Carolina.** Of 934 refugees screened in Cambodia, 916 were resettled to counties in NC by April 2003. Of this group, 821 (90%) submitted at least one stool specimen, and 95% of this latter group submitted three stool specimens. Of the 821 persons who submitted at least one specimen, 783 refugees had received albendazole before departing Cambodia, and 777 (> 99%) of these received five days of treatment. The other six persons received partial or no treatment and were excluded from further analysis. Only one partially treated person had parasites (nonpathogenic protozoa) on stool examination. In addition to the 777 fully treated refugees, the evaluated population comprised an additional 38 pregnant women and children less than two years of age, who were ineligible for treatment.

The age and sex distribution of the 815 refugees is shown in Figure 1. Seventy-six percent of the cohort was male. The age of most refugees (65%) ranged from 19 to 44 years, with only six (< 1%) ≥ 65 years of age. There were 15 pregnant women (1.8%) and 23 (2.8%) children less than two years of age. The demographics of the evaluated refugees were similar to the remainder of refugees who did not submit stool specimens or were resettled to other areas of the United States.

**Impact of overseas pre-departure treatment on parasitic infection rates.** Table 1 shows the results of the NCSLPH

![Figure 1](image-url)  
**Figure 1.** Age and sex distribution of the 815 refugees.
Prevalence of parasitic infection by category in refugees receiving overseas pre-departure treatment compared with untreated refugees, North Carolina State Laboratory for Public Health (n = 815), 2002–2003

<table>
<thead>
<tr>
<th>Category</th>
<th>Treated population, no. (%)</th>
<th>Untreated population, no. (%)</th>
<th>Significance using Fisher’s exact test*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pregnant women, no. (%)</td>
<td>Children &lt; 2 years of age, no. (%)</td>
<td>Total, no. (%)</td>
</tr>
<tr>
<td><strong>Helminths‡</strong></td>
<td>10 (1.3)</td>
<td>3 (20.0)</td>
<td>0</td>
</tr>
<tr>
<td>Pathogenic or potentially pathogenic protozoa†</td>
<td>65 (8.4)</td>
<td>1 (6.7)</td>
<td>0</td>
</tr>
<tr>
<td>Pathogenic protozoa and helminths†</td>
<td>1 (0.1)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Non-pathogenic protozoa‡</td>
<td>136 (17.5)</td>
<td>2 (13.3)</td>
<td>0</td>
</tr>
<tr>
<td>No parasites found</td>
<td>565 (72.7)</td>
<td>9 (60.0)</td>
<td>23 (100)</td>
</tr>
<tr>
<td>Total</td>
<td>777</td>
<td>15</td>
<td>23</td>
</tr>
</tbody>
</table>

* P value refers to the comparison between treated and untreated (children < 2 years of age and pregnant women) refugees. Fisher’s exact test was used to compare the differences between the treated and untreated group. When the number of expected cases was > 5, χ² analysis was used.
† The numbers of refugees who had pathogenic or potentially pathogenic protozoa and/or helminths include those with concomitant nonpathogenic protozoa.
‡ Those refugees who are classified as having nonpathogenic protozoa did not have any pathogens.

microscopic examinations for intestinal parasites in the fully treated and untreated refugees. To evaluate the impact of overseas pre-departure treatment on parasitic infection rates, the prevalence of parasites among refugees who received overseas pre-departure albendazole treatment for five days was compared with that of untreated refugees. Fully treated refugees had a significantly lower prevalence of helminths (11 % of 777) compared with untreated pregnant women (3 % of 78). The prevalence of helminths among treated nonpregnant women (0 of 78) and treated men (10 % of 470) in the same age range as the untreated pregnant refugees (18–47 years) was significantly lower than that in pregnant women (P < 0.01) (Tables 1 and 2). The prevalence of helminths among treated nonpregnant women (0 of 78) and treated men (10 % of 470) in the same age range as the untreated pregnant refugees (18–47 years) was significantly lower than that in pregnant women (P < 0.01) for both comparisons. There were no helminthic infections among treated children less than 17 years of age, and the prevalence was 1.9% among treated adults, a difference that approached but did not reach statistical significance (P = 0.08) (Table 3). No parasites were found in any specimens of children less than 2 years of age.

Species-level analysis showed that untreated pregnant women were more likely to have helminths such as Ascaris and hookworm (3 % of 15) than were treated refugees (0 of 777) (Table 2). The prevalence of protozoan infections was nearly the same in the treated and untreated populations. Children (< 18 years of age) had a higher prevalence of G. intestinalis infection than adults ≥ 18 years of age, but the prevalence of infection with nonpathogenic protozoa and helminths was similar (Tables 3 and 4). Results of a multivariate logistic regression analysis show that treatment, independent of age and sex was associated with significantly lower rates of helminthic infection (Table 4). Sex was not associated with parasitic infection.

We also considered other potential risk and confounding factors for parasitic infection related to our methods of assessment, including the number of stool specimens collected, time between treatment and stool collection, and use of a different fixative for preparation of specimens from asymptomatic refugees. Although different rates of parasitic infection in refugees submitting one, two, and three stool specimens for laboratory examination may have been expected, 95% of the refugees in our group submitted three stool specimens. Thus, the distribution was insufficient for meaningful comparisons. Similarly, although the time intervals between treatment in Cambodia and arrival in North Carolina and between arrival in North Carolina and submission of stool specimens could have been important, the time between treatment and arrival and between arrival and stool examination was less than two months for most refugees. In addition, although the yield of the stool examination for intestinal parasites was not increased for specimens preserved in LV-
PVA, the number of specimens submitted in LV-PVA was small. Among 491 treated refugees who responded to the questionnaire and submitted stool specimens, 192 (39%) reported at least one gastrointestinal symptom. The most common symptom was abdominal pain (25%), followed by weight loss (11%), nausea/vomiting (10%), diarrhea (5%), and bloody stools (4%). Among the 491 refugees evaluated for symptoms, 455 (92.7%) had no parasites or only nonpathogenic protozoa found on microscopic examination; 36 (7.3%) had a pathogenic or potentially pathogenic parasite identified. Twenty-six of the 36 symptomatic refugees with parasites in their stool had *G. intestinalis*, and of these, 6 (23%) persons had abdominal pain, 3 had weight loss (11%), 1 had nausea/vomiting, and 1 had diarrhea (4%). None had bloody stools. Rates of symptoms were not statistically significantly different in refugees with and without *G. intestinalis* infection. For identifying pathogenic intestinal parasite infection, the reporting of any gastrointestinal symptom had a sensitivity of 36%, a specificity of 55%, a PPV of 7%, and an NPV of 92%. There were no significant associations between any one of the symptoms reported and the presence of any pathogenic intestinal parasite.

**Laboratory quality assurance.** From the specimens evaluated by the NCSLPH in the evaluation period, CDC examined all 195 positive specimens and 49 randomly selected negative specimens. Among negative specimens, results for 46 (94%) of 49 were concordant. Of the three discordant specimens, one was not analyzed because there was no identification number for the CDC laboratory, one had 1+ *B. hominis*, and one specimen had rare hookworm. Among positive specimens, results from CDC and NCSLPH were concordant in 129 (66%) specimen sets and discordant in 66 (34%) specimen sets. More than half (36 or 54%) of discordant results involved identification of nonpathogenic protozoa. Using CDC’s results as the reference, the specificity and NPV of NCSLPH examinations were high (> 96%). Sensitivity was 100% for most pathogens, greater than 90% for the most prevalent pathogen, *G. intestinalis*, and 100% for all the helminths except *Ascaris lumbricoides* (identified by both CDC and NCSLPH in one sample and by only one laboratory in each of two other samples). *Strongyloides stercoralis* was identified by NCSLPH in three samples but in none by CDC. Because results were similar between the two laboratories and CDC did not examine the specimens collected after August 31, 2002, the NCSLPH findings were used for the analysis.

**DISCUSSION**

We attempted to determine the impact of overseas pre-departure treatment with albendazole for five days by comparing the prevalence of intestinal parasitic infection in treated and untreated refugees shortly after their arrival in the United States. Although the pre-departure prevalence of infection is not known and the number of untreated persons in our sample was small, overseas treatment with albendazole for five days appears to have been effective against certain helminth infections. Rates of infection with *A. lumbricoides* and hookworm were significantly lower among treated more than two years of age than in untreated persons the same age. This is an expected finding because even one dose of albendazole can achieve cure rates > 90% against these organisms.16 The prevalence of infection with *S. stercoralis* among treated persons in our population was also low (0.4%), but we cannot comment on the effectiveness of treatment because none of the small group of untreated persons had this infection for comparison. No significant differences were seen between the treated and untreated groups with respect to infection with *Hymenolepis nana* and *Taenia* species, other pathogens for which longer courses of albendazole may have some effectiveness.

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**TABLE 3**

Prevalence of helminthic and pathogenic protozoan infections by species in 594 treated adults and 183 treated children as evaluated by the North Carolina State Laboratory for Public Health*

<table>
<thead>
<tr>
<th>Parasite category and species</th>
<th>Treated adults ≥ 18 years of age, no. (%)</th>
<th>Treated children 2–17 years of age, no. (%)</th>
<th>Significance using Fisher’s exact (χ²)</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Helminths</em></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Ascaris lumbricoides</em></td>
<td>11 (1.9)</td>
<td>0</td>
<td>0.08</td>
</tr>
<tr>
<td><em>Hookworm</em></td>
<td>0</td>
<td>0</td>
<td>NA</td>
</tr>
<tr>
<td><em>Hymenolepis nana</em></td>
<td>5 (0.84)</td>
<td>0</td>
<td>0.60</td>
</tr>
<tr>
<td><em>Strongyloides stercoralis</em></td>
<td>3 (0.51)</td>
<td>0</td>
<td>0.0</td>
</tr>
<tr>
<td><em>Taenia</em> species</td>
<td>3 (0.51)</td>
<td>0</td>
<td>1.0</td>
</tr>
<tr>
<td><em>Pathogenic/potentially pathogenic protozoa</em></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Entamoeba histolytica/dispar</em></td>
<td>4 (0.67)</td>
<td>1 (0.55)</td>
<td>&lt;0.01 (χ²)</td>
</tr>
<tr>
<td><em>Giardia intestinalis</em></td>
<td>31 (5.2)</td>
<td>29 (15.9)</td>
<td>&lt;0.01 (χ²)</td>
</tr>
<tr>
<td><em>E. histolytica/dispar</em> and <em>G. intestinalis</em></td>
<td>1 (0.17)</td>
<td>0</td>
<td>1.0</td>
</tr>
</tbody>
</table>

* NA = not applicable.

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**TABLE 4**

Multivariate logistic regression analysis of selected risk factors for parasitic infection (n = 815)

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Comparison groups</th>
<th>Odds ratio (95% confidence interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Helminths</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treatment</td>
<td>Untreated compared with treated</td>
<td>7.19 (1.81–28.56)</td>
</tr>
<tr>
<td>Age</td>
<td>&lt; 18 years of age compared with ≥ 18 years of age</td>
<td>Undefined*</td>
</tr>
<tr>
<td>Sex</td>
<td>Female compared with male</td>
<td>0.71 (0.18–2.76)</td>
</tr>
<tr>
<td><strong>Pathogenic/potentially pathogenic protozoa</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treatment</td>
<td>Untreated compared with treated</td>
<td>0.30 (0.04–2.23)</td>
</tr>
<tr>
<td>Age</td>
<td>&lt; 18 years of age compared with ≥ 18 years of age</td>
<td>2.95 (1.70–5.13)</td>
</tr>
<tr>
<td>Sex</td>
<td>Female compared with male</td>
<td>1.09 (0.60–1.98)</td>
</tr>
<tr>
<td><strong>Non-pathogenic protozoa</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treatment</td>
<td>Untreated compared with treated</td>
<td>0.24 (0.06–0.999)</td>
</tr>
<tr>
<td>Age</td>
<td>&lt; 18 years of age compared with ≥ 18 years of age</td>
<td>1.04 (0.66–1.63)</td>
</tr>
<tr>
<td>Sex</td>
<td>Female compared with male</td>
<td>1.44 (0.93–2.25)</td>
</tr>
</tbody>
</table>

* There were no helminths in refugees < 18 years of age.
Despite the small number of untreated persons in our study, the prevalence of infections with *A. lumbricoides* and hookworm were similar to that of untreated refugees from Southeast Asia who were resettled in Illinois and Minnesota around the same time as our study.4,9 *Strongyloides* infection was also infrequent in these other refugee groups: 3.4% and less than 1% of refugees resettled in Illinois and Minnesota, respectively, had this parasite detected in their stool.4,9

Although a five-day course of albendazole has been effective for treating *G. intestinalis* infections in a number of studies;17–19 rates of infection were similar for treated adults (5.4%) and untreated pregnant women (6.7%). The higher prevalence of *G. intestinalis* infection among children (15.9%) may reflect a higher pretreatment prevalence or reinfestation after treatment. Hand-to-mouth behavior places children at greater risk for giardiasis, and adults may have partial immunity from repeated exposures. Similar rates of infection with *E. histolytica/dispar* and nonpathogenic protozoa in our treated and untreated groups is not surprising because albendazole is not active against these organisms.

We found that reported symptoms were not correlated with findings of intestinal parasites in stool examination. Other studies have shown similar results, even in refugee and immigrant populations that had not received presumptive treatment and had higher rates of infection.5,20

In general, the concordance in results of stool examinations from the CDC laboratories and NCSLPH was excellent. Low intensity of infection and the known insensitivity of stool examination with *S. stercoralis* most likely contributed to the different results from the two laboratories.

We were unable to collect and test pre-departure specimens because of the urgency of resettlement, and pre-departure rates of infection may have been low because the refugee camp where our population stayed for a year provided relatively clean water and medical treatment. Another limitation of our study is that the untreated (children < 2 years of age and pregnant women) and untreated groups were not directly comparable. Pregnant women, as well as young children, may be at greater risk of infection for immunologic and behavioral reasons (e.g., pica).21

Future studies should compare the current policy of presumptive treatment of Southeast Asian refugees with a one-day course of albendazole with a five-day course and with the combination of one dose of albendazole with one or two doses of ivermectin, which is active against *Strongyloides*. Better information about likely infection rates with various pathogens would indicate whether short or longer courses of albendazole with or without adjunctive therapies would provide benefit. Adding a dimension of prevention effectiveness to the analysis will also be important to guide policy. We elected to treat with albendazole for five days on the basis of an analysis of hypothetical situations that showed greater cost-effectiveness for presumptive treatment than for universal screening and targeted treatment or watchful waiting when the prevalence of *Strongyloides* was greater than 16% or a combined prevalence of *A. lumbricoides*, hookworm and *Trichuris trichiura* was greater than 65%.9 Previous work suggests that the direct dollar costs of state-side screening are higher than the costs of disease prevented in asymptomatic Southeast Asian adult refugees,27 but models using social utility23 and other factors, and information on disease prevalence as well as treatment prior to departure would change the analysis.

Further data are also needed to guide recommendations for pregnant women and children less than two years of age. The World Health Organization recommends single-dose albendazole for infected pregnant women24 and children as young as one year of age25 because of its positive impact on nutrition, growth, infant mortality, birth weight, and hemoglobin level. Children less than two years of age are often excluded from mass treatment programs; however, once they become mobile, they are likely to be at risk for parasitic infection. Increasing experience throughout the world has demonstrated the safety of albendazole in these two groups, especially in pregnant women. Although albendazole is teratogenic in rats and rabbits, cross-sectional and prospective controlled trials show minimal risk of albendazole and mebendazole to pregnant women, even in the first trimester.26–32 In one study of pregnant women refugees in camps with access to adequate nutrition, monitoring, and medical care, deferring treatment during pregnancy did not result in adverse health effects,33 and the risk of adverse effects can be expected to decrease after migration from a parasite-endemic area.

In conclusion, this evaluation was a unique opportunity to design and implement an enhanced refugee health assessment in a partnership composed of CDC, IOM, the North Carolina Division of Public Health, including the Communicable Disease Program, Refugee Health Program, and Laboratory for Public Health, and five local health departments in North Carolina. The results of our evaluation of the impact of pre-departure treatment among Vietnamese Montagnard refugees in the context of an urgent refugee resettlement suggest that a five-day course of pre-departure albendazole treatment was effective in reducing helminthic infection.

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Disclosure: J. Jina Shah is currently working for Novartis Vaccines. Work for this paper was done prior to employment with Novartis, and there is no conflict of interest.

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