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Study design and baseline results of an open-label cluster randomized community-intervention trial to assess the effectiveness of a modified mass deworming program in reducing hookworm infection in a tribal population in southern India

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A B S T R A C T

Introduction: Hookworm infection is a leading cause of iron deficiency anemia and malnutrition in resource-poor settings. Periodic mass deworming with anthelminthic drugs remains the cornerstone of hookworm control efforts worldwide. Reinfection following treatment occurs, reflecting the human host's inability to acquire immunity following exposure to an untreated reservoir of infection. This cluster randomized trial will evaluate the effectiveness of a modified, population-based, mass deworming strategy in reducing hookworm infection in an endemic southern Indian population.
Methods: Forty five tribal villages were randomized into three groups: one received annual treatment; the second received two rounds of treatment at 1-month intervals; and the third received four rounds of treatment – two rounds 1 month apart at the beginning, followed by another two after 6 months. Stool samples collected through cross-sectional parasitological surveys pre- and post-intervention, and at 3-monthly intervals for a period of 1 year were tested for presence of hookworm ova. Long-term effectiveness of treatment will be assessed through another survey conducted 2 years after the last treatment cycle.
Results: From a population of 11,857 individuals, 8681 (73.2%) were found to be eligible and consented to participate, out-migration being the primary reason for non-participation. Baseline stool samples were obtained from 2082 participants, with 18.5% having hookworm infection, although majority were low intensity infections (<2000 eggs per gram of feces).
Discussion: This study will help identify the optimal mass deworming strategy that can achieve the greatest impact in the shortest period of time, particularly in settings where long-term program sustainability is a challenge.

1. Introduction

Hookworms, along with the other soil transmitted helminths (STH), *Ascaris lumbricoides* and *Trichuris trichuira*, are among the commonest gastrointestinal infections in humans [1]. Hookworms

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affect an estimated 438.9 million people worldwide, resulting in 3.2 million disability adjusted life years (DALY) [2]. This exceeds the disability burden of most other tropical diseases [3,4]. Most human hookworm infections are caused by two species - *Necator americanus* and *Ancylostoma duodenale*, although considerable regional variation in the species composition has been described [5]. There is a clear relationship between hookworm prevalence and low socioeconomic status, with the majority of "at risk" population living on less than US$2 per day [6,7].

In children, hookworm infections are associated with iron-deficiency anemia, stunted growth, poor nutritional status and reduced physical and cognitive abilities, and therefore may profoundly impact school performance and future economic productivity [8,9]. Increasing hookworm infection intensity is also associated with lower hemoglobin levels in adults, particularly in pregnant women living in low-income countries [10,11].

The World Health Organization (WHO) has set a global target of regularly treating at least 75% of the pre-school and school-aged children in endemic areas through school-based deworming programs to eliminate morbidity due to STH by 2020 [12]. Despite high cure rates [13,14], failure to prevent reinfection even after effective treatment is a recognized shortcoming of this strategy [15–18], often due to an untreated reservoir of infective stages in the environment. In a meta-analysis, a 30% reinfection rate was observed at 3 months post-treatment, increasing to 57% at 12 months [19]. A positive correlation between pre-treatment infection intensity and reinfection status has also been noted [18]. Moreover, recent modeling-based estimates suggest that school-based deworming may have limited impact in interrupting the community transmission of STH infections, especially in places where hookworm predominates because most infection is harbored by adults [20]. The transmission of an infectious agent following drug treatment is a dynamic process, and is determined by many factors including treatment frequency, coverage and efficacy [21,22]. Suboptimal treatment may result in persistence of an untreated reservoir of transmission, thereby increasing the likelihood of reinfection [23] and the need for periodic treatments to interrupt transmission in endemic communities [24]. This, in turn, raises the question of long-term sustainability of such programs and the possibility of emergence and spread of drug resistance [25,26]. There is a need for studies comparing different regimens of mass drug administration (MDA) against hookworm infection to identify optimal deworming strategies that can minimize morbidity or interrupt transmission, thereby enabling the MDA to be stopped.

The primary objective of this study is to compare the hookworm reinfection rates between a population-based MDA strategy of an annual treatment cycle (with albendazole) with two and four cycles of treatment respectively, for a period of 1 year in an endemic tribal population in southern India [27]. The secondary objective is to identify individual, household, community and spatial correlates of infection; and to develop predictive models to understand the dynamics of hookworm transmission in endemic populations. The highly aggregated nature of worm distribution within human communities and predisposition to reinfection among those heavily infected is well established [20,28].

2. Materials and methods

2.1. Study setting

This ongoing study is being conducted in the Jawadhu Hills (JH) block, at the borders of Vellore and Tiruvannamalai districts of Tamil Nadu in southern India (Fig. 1), with a population of about 80,000, mostly tribal with a common ancestry. It has 11 panchayats with about 250 villages; each village has between 15 and 100 households. The community is predominantly agrarian, cultivating rice, millet and maize; pig rearing is a common practice. During non-agricultural seasons, many people migrate to coffee plantations in the neighboring states as short-term (temporary) laborers.

The area has a hilly terrain with poor road access, lack of safe drinking water and poor sanitation facilities. It is endemic for lymphatic filariasis, and all residents aged >1 year are under a mass treatment program with annual co-administration of diethylcarbamazine (DEC) and albendazole since 2007, as part of the Government of India (GoI) initiative to eliminate lymphatic filariasis [29]. Despite this, a cluster survey of 1237 subjects from 680 households in 2011 found a very high hookworm burden, with an overall prevalence of 38%. As is typical for hookworm infection, the prevalence and intensity of infection increased with age [27].

2.2. Study design

The study is an open-label, cluster randomized, community-intervention trial. A total of 45 villages (clusters) with similar population structure, water supply and sanitation practices were selected. The villages were randomized into one of three groups (Fig. 2):

1. Single cycle (15 villages): Village residents of all ages in this group received only one cycle of 400 mg albendazole, at month 1.
2. Two cycles (15 villages): Village residents of all ages in this group received two cycles of 400 mg albendazole at 1 month interval, at month 1 and 2.
3. Four cycles (15 villages): Village residents of all ages in this group received two cycles of 400 mg albendazole at month 1 and 2, followed by another two cycles at month 8 and 9 (a total of four cycles).

The timing of the MDA cycles in the 2- and 4-cycle groups is based on the hookworm biology. The released rhabditiform larvae take about 5–10 days in the soil to become the infective filariform (third-stage) larvae [30]. Hence, it was hypothesized that a second MDA cycle (in the 2-cycle group) covering the extrinsic incubation period will reduce reinfection from the infective larvae already present in the soil. However, as the larvae are known to survive in soil for weeks under favorable environmental conditions [31], it was speculated that these two treatment cycles may not be adequate to achieve transmission breakpoint in endemic settings; therefore another intervention group (the 4-cycle group) with two additional MDA cycles after 6 months was added (Fig. 2). Moreover, multiple treatment cycles will result in an overall increase in MDA coverage and a subsequent reduction in worm intensity, thereby reducing the need for repeated treatments.

2.3. Interventions

All study groups received albendazole 400 mg, an anthelminthic drug that is highly efficacious against hookworm infection [13]. The only difference between the three study groups is the frequency of treatment, which is outlined in Fig. 2. In order to mimic the population-based MDA campaigns initiated by the GoI for elimination of lymphatic filariasis [29], designated deworming days were planned for each village and the residents informed well in advance. Everyone present in the village, who were otherwise eligible and provided written informed consent, were administered a single dose of albendazole 400 mg through door-to-door household visits. A mop-up campaign was conducted the subsequent day to ensure maximum coverage. Participants were interviewed the subsequent day to record details of tablet consumption, and