

Proposal: Initial Planning Grant to Evaluate the Long-Term Impact of Deworming on Community and Household Income, Consumption and Health

Soil-transmitted helminths are among the most frequent infections of humans¹. These parasitic infections are common in areas of the world where access to clean environmental conditions and water, as well as adequate sanitation facilities, are often limited. These conditions are found in areas of extreme poverty, resulting in substantial inequities in the burden of these diseases. In fact, all of the over 3 million disability-adjusted life years attributed to STH occur in low and middle-income countries². Strong evidence exists demonstrating the negative impacts of these infections on human health and societal development. In particular, heavy infections with these parasites have been shown to result in significant anemia, reduced linear and ponderal growth, impaired cognitive development and ultimately lower income earning potential¹.

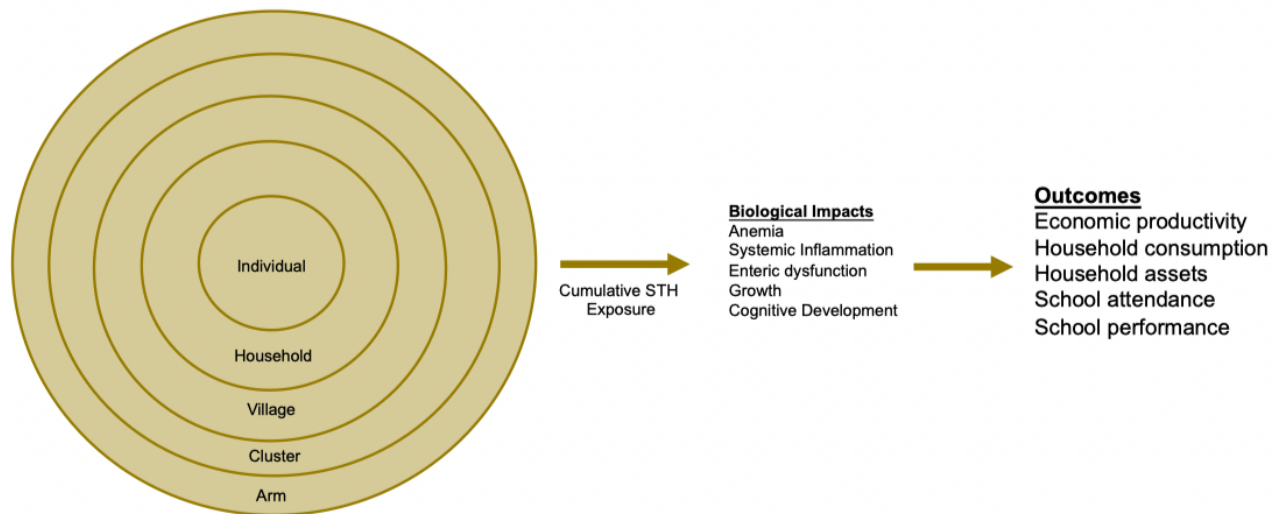
The current World Health Organization endorsed strategy for managing STH infections relies primarily on the delivery anthelmintic drugs through mass drug administration. This strategy is based on the empiric treatment of high-risk populations without initial testing to determine infection status. Such programs have achieved relatively high coverage in many STH endemic communities and have been associated with dramatic reductions in the prevalence and intensity of infection among treated population groups³.

Despite remarkable increases in coverage of MDA programs over the past decade, evidence for long-term population level impacts on health and/or development outcomes has been mixed. Pooled estimates of effect from analyses conducted by the Cochrane collaboration as well as independent researchers suggest limited to no significant benefit from deworming programs on health outcomes including growth and development^{6,7}. However, there has been significant controversy regarding the interpretation of these data given concerns regarding the power of available studies, variability in study design, the short duration of follow up in many studies and other methodological concerns surrounding existing data. In addition, many studies have been conducted in populations in which most individuals are not infected, thereby diluting the potential benefit observed at the population level^{4,5}. More conclusive and precise estimates of the impact of deworming programs on health and economic outcomes are urgently needed to calculate cost-effectiveness and to inform policy and funding priorities.

Among the major limitations of current MDA programs is the rapid rate in which target groups are reinfected following treatment. Because programs primarily target pre-school and school age children, a large reservoir of infections remains in the adult population, who usually remain untreated. This is particularly true for hookworm infections, for which infection prevalence peaks in young adulthood⁸. In addition, hookworm infections are associated with significant reductions in hemoglobin concentrations, particularly among children and women of reproductive age. Hookworm infection may directly impact brain development, linear and ponderal growth, school performance and economic productivity through the development of anemia. Antenatal anemia, which is often associated with hookworm infection, has also been associated with poor birth outcomes, including preterm birth, low birthweight, intrauterine growth retardation and early infant death⁹.

Studies suggest that treating entire populations through community-wide MDA programs may be a more effective method of reducing population prevalence of infection. In addition, modeling studies suggest that repeated rounds of community-wide MDA may be able to interrupt the transmission of STH infection in some communities, and over time, result in the elimination of STH infections from entire populations^{10,11}.

The Bill & Melinda Gates Foundation has supported a large multi-country community cluster-randomized trial of community-wide MDA to determine the feasibility of such an approach in interrupting the transmission of STH (the DeWorm3 trial)¹². Over 370,000 individuals in defined administrative areas in Benin, India and Malawi have been randomized by cluster to receive either standard-of-care or community-wide deworming for a period of three years. An annual census was conducted in each site in which every household and structure was geolocated and detailed socio-demographic data were collected on individuals in each household. Detailed costing data were also collected to determine both economic and non-financial costs incurred from the perspective of the individual and the STH program. In addition, a subset of individuals in India and Benin were followed longitudinally to assess infection status over a five year timeframe. The DeWorm3 trial concluded three years of treatment with exceptionally high coverage and will do a final assessment of infection status in each of the three countries in late 2022. This trial offers a unique and exceptional opportunity to understand the impact of deworming at the individual, household and community level over time in areas where treatment history is well documented.

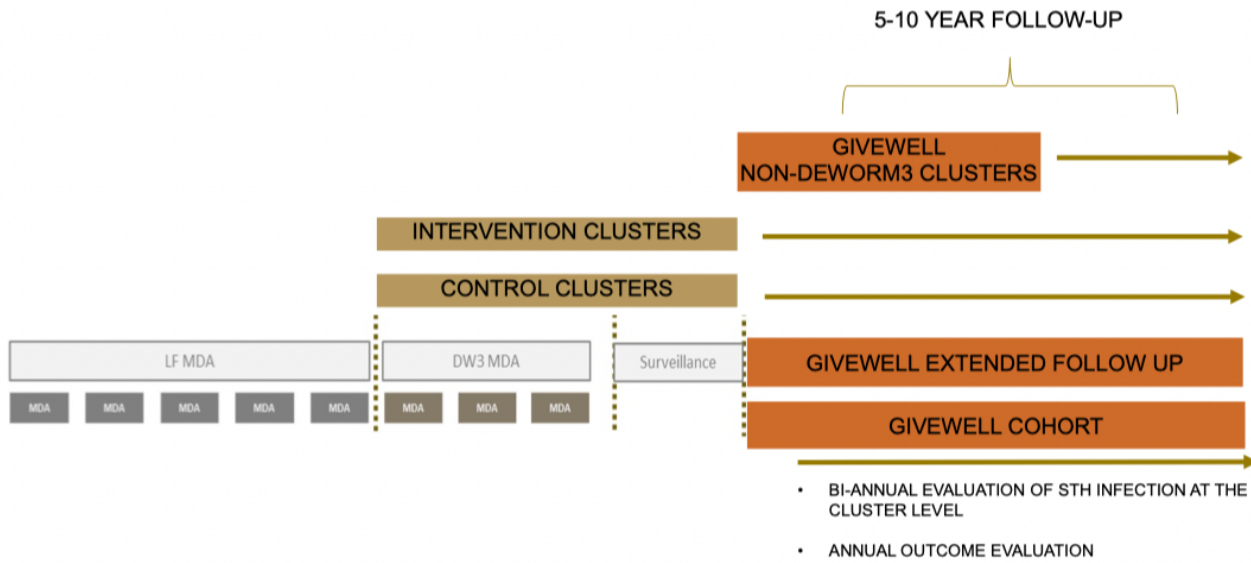


Even with a large sample size such as was included in the DeWorm3 trial, there are questions about the feasibility of designing an adequately powered study to assess the impact of deworming on economic and health outcomes. Because deworming is a relatively inexpensive intervention, supported by a robust global drug donation program and typically delivered through existing school systems, the magnitude of impact likely to result in the intervention being highly cost-effective is quite small. As a result, it is not clear that an adequately powered study can be designed to be practical or within a reasonable budget.

We propose a planning grant to develop a protocol to assess the long-term impact of deworming on household consumption and assets, as well as key health indicators that may be important determinants in the pathway between helminth infection and economic outcomes. These include anthropometry, markers of systemic inflammation, hemoglobin and hematocrit and biomarkers of enteric function and inflammation. We believe that leveraging the DeWorm3 trial will increase both the feasibility and reduce the potential cost of such a trial. We believe that it may be possible to utilize the randomization within the DeWorm3 clusters to assess outcomes based on the time individuals are exposed to infection. By leveraging the cluster randomized design, coupled with the inclusion of neighboring communities not treated by the trial, we may be able to design a highly efficient trial to assess these outcomes. In addition, the inclusion of a longitudinal cohort of individuals may add additional strengths and power to this design. Given the constraints noted above, careful attention to study design, including the use of trial simulations, is needed to determine if and how such a study could be successfully conducted. In particular, we will explore the potential for an adaptive trial that

would be evaluated with early outcome measures to determine the likelihood of success in order to inform continuation. Such adaptive trial design allows for early termination of a trial if the likelihood of observing benefit is below a pre-specified threshold. We are currently conducting an adaptive trial of interventions to improve childhood survival and growth and our experience suggests that this design may be optimal for a possible study evaluating the long term impact of deworming as well.

I LEVERAGE DEWORM3 FOR LONG TERM EVALUATION



For the planning grant, we propose the following;

- Initial background research to finalize study outcomes and optimize inputs into power calculations from existing data, including data from DeWorm3.
- Conducting a two-day study design consultation workshop in which we will invite key clinical trial, health economists, public health and helminth experts. The DeWorm3 study was designed using similar methodology and this was a highly efficient and successful process.
- Trial simulations to ensure that the design parameters agreed upon by the expert workshop participants are likely to result in success, including the possibility of an adaptive trial design.
- Production of a final trial protocol to be submitted to GiveWell for evaluation and consideration for implementation.

Budget

(See attached)

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