A conversation with DeWorm3, March 20, 2018

Participants

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Note: These notes were compiled by GiveWell and give an overview of the major points made by DeWorm3.

Summary

GiveWell spoke with Dr. Walson and Ms. Means of DeWorm3 as part of its investigation into deworming-related research. Conversation topics included an overview of DeWorm3, the progress it has made, and the possibility of including additional outcome measures in its studies.

Overview of DeWorm3

Soil-transmitted helminthiasis (STH) is typically treated through school-based deworming programs, which control the effects of STH but do not interrupt its transmission. DeWorm3, a project of the Natural History Museum in London, is investigating the feasibility of interrupting STH transmission through community-wide mass drug administration (MDA).

Relevant studies

A systematic review conducted by Clarke et al. and published in *The Lancet* in 2016 found that community-wide deworming had a significantly larger impact on STH prevalence and intensity than targeted deworming interventions such as school-based deworming. A study conducted by Lo et al. and published in *The Lancet Global Health* in 2015 found that community-wide deworming was significantly more cost-effective than targeted deworming.

Progress

Definition of STH elimination

DeWorm3's first core objective was to define, both epidemiologically and operationally, what it means to interrupt transmission of STH. It has now published protocols outlining a process for identifying and measuring STH elimination.

Trials in India, Benin, and Malawi

DeWorm3 has begun conducting five-year-long cluster randomized controlled trials (RCTs) in India, Benin, and Malawi. The RCTs are only treating STH, as schistosomiasis (another type of parasitic worm infection) is not a significant problem in targeted areas.

DeWorm3 has enrolled over 370,000 individuals across the three countries, with 20 control clusters and 20 treatment clusters per country. Each cluster represents approximately 2,000 to 5,000 individuals.

The RCTs are still in an early stage, with MDA having commenced only in India. DeWorm3 will not know whether its RCTs are able to achieve STH elimination until two years after it ceases treatment.

Study design

Control clusters will receive standard treatment, which is typically school-based deworming in most areas. However, the standard of care in India is campaign-based deworming, with certain days designated for mass treatment in schools and other locations. Coverage rates for standard treatment also differ across countries. For example, although national guidelines for Benin indicate that preschool-aged children should be dewormed, very little outreach is conducted to target this population. In practice, only school-going children receive deworming treatment in Benin, and the country experiences low school participation rates (particularly for females). Therefore, control clusters in Benin will likely include a significant number of untreated individuals. Control clusters in India, however, will likely experience higher treatment coverage due to stronger national efforts to target both preschool and school-aged children.

Treatment clusters will receive community-wide, biannual MDA for individuals aged one and above.

DeWorm3 believes that its RCTs may result in a few different outcomes. One potential outcome is that STH transmission is successfully interrupted in treatment clusters, and control clusters continue to receive school-based deworming. Another potential outcome is that STH transmission is not interrupted in treatment clusters. In the latter case, treatment clusters would eventually return to receiving school-based deworming after the community-wide MDA program ceases, and any differences in STH prevalence between treatment and control clusters would become much smaller.

Baseline data collection

DeWorm3 has conducted censuses, sampling 100,000 to 130,000 people per country. Information gathered includes number of households, number of individuals per household, and migrant versus resident population.

DeWorm3 has also conducted assessments of baseline prevalence and intensity of STH in each RCT cluster for each country, a total of 120 clusters. Country-level STH prevalence is as follows:

- **India** – Country-level prevalence of having any STH in India is approximately 15% and composed mainly of hookworm infection. However, STH prevalence is highly variable across different clusters, with

some clusters experiencing 2-3% prevalence and others (particularly in tribal areas) experiencing 40-50% prevalence.
- **Benin** – Country-level prevalence of having any STH in Benin is approximately 9% and composed mainly of ascariasis (4.5%) and hookworm infection (4.3%), with a small level of trichuriasis prevalence.
- **Malawi** – Country-level prevalence of having any STH in Malawi is 4-7% and composed mainly of hookworm infection. Although STH prevalence is low, it is not sufficiently low to discontinue Malawi's deworming program. The World Health Organization (WHO) recommends ceasing deworming treatment when STH prevalence declines to 1-2%, although these guidelines are unclear and often not followed.

DeWorm3's current estimates for baseline STH prevalence were computed using the Kato-Katz technique. It expects that prevalence estimates will increase by 50-100% when using the quantitative polymerase chain reaction (qPCR) technique, which is able to better account for low-intensity infections.

Research on community-based implementation model

DeWorm3 is conducting ongoing research on the optimization of and barriers to community-wide MDA programs. The Ministry of Education is often the governmental department responsible for deworming, as many countries currently operate MDA programs through schools. A community-based MDA model, however, is more likely to be the responsibility of the Ministry of Health, a change that can have numerous political and financial consequences.

DeWorm3 has received funding from the Children's Investment Fund Foundation to conduct more research on how to optimize and scale up community-wide programs.

Potential inclusion of additional outcome measures

Morbidity outcomes

Currently, DeWorm3's only outcome measure for its RCTs is the interruption of STH transmission. It did not design or statistically power the studies to be able to detect differences in morbidity outcomes, as it did not want its core goal to be misinterpreted.

In the absence of additional funding, DeWorm3 will not measure the impact of its interventions on growth and cognition. However, it does plan to measure its impact on certain morbidity-related outcomes, such as anemia. DeWorm3 will not collect baseline data for these outcomes, as it assumes that its randomization process resulted in approximately equal distributions of disease across treatment and control groups.

Challenges for including morbidity outcomes

Since its study designs have now been completed and submitted, DeWorm3 is no longer opposed to measuring its impact on morbidity-related outcomes such as growth and cognition. However, because the studies have been randomized to

detect STH elimination and not differences in morbidity, these would be secondary outcomes and values for morbidity-related outcome measures may be criticized as low-quality evidence.

DeWorm3 still believes that measuring morbidity outcomes would be valuable and that any strong differences detected in morbidity would be compelling, though it would need additional funding to measure these outcomes.

Benefits of measuring long-term outcomes

Most governments are reliant on external donors and donations from pharmaceutical companies to operate deworming programs. DeWorm3 believes that measuring the impacts of community-wide and school-based deworming programs on long-term outcomes may be valuable to these donors. For example, if DeWorm3 finds no evidence of impact on long-term outcomes, donors may wish to stop funding deworming programs.

Potential measurement of growth and cognition

The two long-term outcomes that DeWorm3 would be most interested in measuring with additional funding are growth and cognition. Since STH reinfection rates for individuals that receive school-based deworming are high, studies that test the impact of school-based deworming on growth and cognition are unlikely to detect any meaningful impact. However, DeWorm3's RCTs or other studies implementing community-wide MDA may provide an opportunity to test whether STH elimination can have long-term impacts on growth and cognition.

Process

DeWorm3 has already identified a subset of 150 individuals per cluster in each of its countries (a total of 6,000 individuals per country) that it will be monitoring more intensively. It will measure the infection status of these individuals every six months during the entire course of the studies and will know how many rounds of deworming treatment the individuals received. If it decides to include growth and cognition as outcome measures for this cohort, DeWorm3 would be able to detect differences in growth and cognition between individuals that consistently received treatment for three years and individuals that received little treatment or were untreated. The sample size of the cohort is sufficiently large to statistically power an analysis of growth and cognition outcomes.

Challenges

Variability in cognition measurement can be high. If the measurement error is higher than actual differences in cognition between dewormed and non-dewormed individuals, detecting a statistical difference in cognition would be difficult.

Reducing the risk of error in both cognition and growth measurement would require intensive measurement conducted by well-trained researchers, which many studies often lack.

Potential measurement of income

DeWorm3 can begin measuring the impact of community-wide MDA on income three to five years into its studies. However, analyzing the long-term impact of STH elimination on income would require follow-up 10 to 20 years after the interventions. To ensure robust estimates for impacts on income, DeWorm3, and not an external group, should conduct measurement.

Currently, DeWorm3 is collecting detailed data on costs. DeWorm3 is unique for its collection of data on costs associated with time expended by caregivers, health workers (particularly volunteer health workers), teachers for school-based deworming programs, and individuals participating in MDA. No study of DeWorm3's scale has collected data on all of these costs. DeWorm3 is also collaborating with modeling professionals from Imperial College London, including Professor Sir Roy Anderson, on evaluation of both short-term and long-term (10-20 years) cost-effectiveness. DeWorm3 would consider adding measurement of long-term income to its economic evaluation model, although it does not currently have the necessary resources.

Process

DeWorm3 would first identify individuals who are not yet earning income, selecting an age range that would be most useful to test the hypothesis that deworming may increase income. It would then select a sample of those individuals and employ a team of specialized researchers to collect data on the baseline characteristics of individuals in the sample. DeWorm3 would then assess these individuals' income at a chosen time interval.

An appropriate sample size sufficiently large to statistically power an analysis of changes in income would be approximately 15,000 individuals (5,000 households), encompassing a five-year age range. Sampling 5,000 households is within DeWorm3's capacity, as it is currently surveying approximately 150,000 households for its RCTs.

Estimated costs

The costs of measuring long-term income would depend significantly on the age range and number of individuals sampled. DeWorm3's very rough approximation of the resources required would be a team of five individuals per country to take measurements as well as central staff to oversee and coordinate the analysis. The central staff would be able to manage data collection for all three countries, reducing overall costs. Baseline data collection would likely occur within the next two years, with following rounds of data collection occurring every five years for approximately 20 years.

DeWorm3 believes a reasonable ballpark cost estimate for measuring long-term income is about $500,000 per country for every round of data collection. It believes income should be measured in all three countries in order to understand the impact of STH elimination across different settings. The countries and some of the clusters

within the countries represent highly heterogeneous contexts both in terms of STH prevalence and types of worms infecting the population (as discussed previously) as well as other factors:

- **India** –DeWorm3's intervention in India is targeting one area composed of extremely poor tribal groups whose needs are not being met by the state government and another area composed of farmers and some merchants who, although poor, are beginning to represent a lower-middle-class in India.
- **Benin** – DeWorm3's intervention in Benin is targeting a peri-urban (hybrid of rural and urban characteristics) area that experiences significant migration.
- **Malawi** – DeWorm3's intervention in Malawi is targeting a rural, agrarian area which has not benefitted significantly from modernization but does have easy access to water and sanitation resources. Income generation in this area mostly occurs through migratory workers traveling to other countries for work in mining or farming.

Timeline for inclusion of additional outcomes

Since DeWorm3 has already begun MDA in India and will begin shortly in Benin and Malawi, additional outcome measures must be added relatively soon in order to capture true baseline values. It may also be important to consider that if DeWorm3 decides to include additional outcome measures, it must submit amendments to institutional review boards in all three countries, which would take one month to six weeks per country.

DeWorm3 believes that including income as an outcome measure is less time-sensitive, as income for targeted populations is unlikely to change significantly over the next year. However, DeWorm3 is concerned that if it takes too long to include growth and cognition as outcome measures, targeted populations will have already been dewormed multiple times, making it highly difficult to estimate baseline values. If DeWorm3 receives funding to measure growth and cognition and can begin measurement in the next few months, it would be able to capture true baseline values in Benin and Malawi before MDA begins in those countries. More realistically, DeWorm3 would like to begin measuring growth and cognition within the next six to eight months in order to be able to capture baseline values before a second round of deworming treatment has begun in any of the three countries.

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