A conversation with Dr. Nathan Lo, April 24, 2017

- Dr. Nathan Lo – MD-PhD Candidate, Stanford University School of Medicine
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Note: These notes were compiled by GiveWell and give an overview of the major points made by Dr. Nathan Lo.

Summary

GiveWell spoke with Dr. Lo, a MD-PhD candidate at Stanford University who specializes in mathematical modeling and economic analysis of neglected tropical diseases. GiveWell conducted this conversation as part of its investigation into the biological consequences of schistosomiasis and soil-transmitted helminth (STH) infections. Conversation topics included health consequences of worm infections, the processes used to estimate disability weights for worm infections, and metrics for tracking the effectiveness of mass drug administration programs.

Health consequences of worm infections

The epidemiologic research on worm infections, especially randomized trials, has primarily focused on short-term health effects. Hypothesis driven research has not focused on testing or teasing out the long-run effects of worm infections or benefits outside of health (e.g. education, economic advancement), aside from work led by Professor Ted Miguel at the University of California, Berkeley.

Treatment of several different types of worm infections is often considered a single development package. This is because multiple types of worm infections (the three soil-transmitted helminths) can be treated with a single drug (albendazole). However, the biological effects on human health from the different worm infections are clinically distinct:

- *Ascaris* infections tend to be minimally invasive and are unlikely to trigger inflammatory responses. Most of the effects of *Ascaris* are acute morbidities that resolve quickly after treatment. Long-term sequelae are rare.
- *Trichuris* and hookworm infections are invasive. These worms burrow into the body's mucosal linings and incite inflammatory immune responses.
- Schistosomiasis infections are invasive and can cause significant inflammatory responses. The clinical effects vary substantially between different species of *Schistosoma,* some of which reside near the liver while others are close to the bladder. In some cases, schistosomiasis infections can lead to potentially fatal complications (e.g. liver fibrosis from *Schistosomiasis mansoni* or bladder cancer from *Schistosoma haematobium*).

Most serious consequences of schistosomiasis and other worm infections are not caused directly by worms. Rather, the body's immune response to infections causes symptoms in some cases.

Experts have speculated that anemia caused by chronic inflammation may be responsible for the long-term consequences of childhood worm infections. In general, STH infections are associated with fewer chronic morbidities than schistosomiasis infections. Inflammation caused by STH infections is often reversible. Schistosomiasis has both acute (and reversible) morbidities, and also chronic (and sometimes irreversible) morbidities.

Relationship between infection intensity and disease severity

There are critical non-linearities in the relationship between worm infection intensity and disease severity. Based on a combination of empirical evidence, expert consensus, and common sense, Dr. Lo expects that worm infections involve both threshold and saturation effects: very light worm infections are unlikely to have serious consequences, and the marginal effect of slightly more worms in a heavily-infected individual's body may be negligible.

Possible adverse effects of eliminating worm infections

Parasitic worm infections have been fairly common throughout human history. Some have hypothesized that the elimination of worms in developed countries has contributed to the rising incidence of autoimmune diseases.

There have been attempts to test this hypothesis experimentally. Participants in randomized controlled trials in the United States have been exposed to helminth eggs to ascertain the effect on the incidence of autoimmune diseases. These studies have found no meaningful relationships. However, one could argue that these trials are limited since they only had adult participants and perhaps only a lack of childhood exposure to chronic worm infections increases the risk of developing autoimmune diseases.

Overall, according to Dr. Lo, society faces a choice between treating diseases with known, avertable morbidities and electing not to treat these diseases on the basis of a hypothesized mechanism for a rare outcome. Dr. Lo believes that the expected benefits of treating worm infections far outweigh the potential costs.

Disability weights

Several approaches have been used to estimate disability weights for worm infections. In the standard approach, symptoms of an infection are described briefly, and individuals are asked how they would tradeoff between different health states. In some cases, disability weights have been estimated by combining the disability weights associated with individual worm infection symptoms. Information about the prevalence and severity of each symptom can be combined to form a single composite disability weight for a given type of worm infection.

There is not substantial evidence for meaningful quality of life improvements from treating light STH infections. Consequently, it has become standard to associate light STH infections with either no disability weight or a disability weight near zero.

Dr. Lo has concerns about the methodologies involved in calculating disability weights across all health states and diseases, but he believes the weights commonly

used for schistosomiasis and STH infections are probably conservative. Dr. Lo's concerns about the disability weights extend beyond worms, although he believes it is a good starting point. Dr. Lo also thinks ongoing work by the Institute for Health Metrics and Evaluation may improve the reliability of disability weights for tropical diseases.

Treatment thresholds

Dr. Lo believes that the standard thresholds set by the World Health Organization and used for determining which populations to treat for worm infections and the frequency with which to treat can be improved. The prevalence thresholds were selected based on expert opinion alone, and while Dr. Lo states that they have advanced deworming, he believes that they should be updated. Dr. Lo would prefer that prevalence thresholds were developed using a cost-effectiveness-oriented approach that draws on the scientific understanding of worm infection dynamics and clinical evidence. Dr. Lo's work published in Lancet Infectious Diseases in 2016 (available here: http://www.thelancet.com/journals/laninf/article/PIIS1473-3099(16)30073-1/abstract) completed this analysis, and found that current prevalence thresholds (especially for schistosomiasis) were too restrictive from a cost-effectiveness perspective. Furthermore, his analysis defined prevalence thresholds for community-wide treatment and formulated guidelines in an integrated fashion, meaning that both STH and schistosomiasis were considered.

Monitoring mass drug administrations

To monitor the success of mass drug administrations (MDAs), it's preferable not to rely on the prevalence of infection in a population. When possible, one should track mean egg intensity. Mean egg intensity is closely associated with disease severity and tends to drop quickly following MDAs. Infection prevalence tends to remain relatively robust following MDAs. Since egg intensity is closely associated with disease severity, it's better to rely on that metric when it's available.

Dr. Lo believes that making substantial changes to MDA strategies based on a decline in prevalence level alone can be a mistake. If MDAs bring down infection levels from the baseline, ceasing treatment or reducing treatment frequency may allow infections to return to baseline levels.