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CONTROLLING SOIL-TRANSMITTED HELMINTHS: TIME TO THINK INSIDE THE BOX?

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ABSTRACT: Soil-transmitted helminths (STH) refer to several parasitic nematode species that infect over 1 billion people worldwide. Infections with *Ascaris lumbricoides*, *Trichuris trichiura*, and the hookworms *Necator americanus* and *Ancylostoma duodenale* cause significant morbidity in more than 450 million people, primarily children and pregnant women, resulting in over 39 million disability-adjusted life years lost. Considerable effort and resources have been, and continue to be, spent on top-down, medical-based programs to control STH infections, with little success. This review discusses the problems with these methods and proposes a new emphasis on sustainable, long-term investments in sanitation-based approaches using improved latrines (the "box") to provide bottom-up, culturally appropriate, and economically desirable solutions to STH control in endemic areas. One such approach is the use of biogas technology. Waste undergoes fermentation in specially designed septic systems, generating a methane gas mixture ("biogas") that can be burned to augment or replace household energy needs such as cooking and light generation. Also, the effluent from the fermentation chamber provides a high quality, nitrogen rich fertilizer. Using China as an example, the use of biogas technology as a solution to rural sanitation and energy problems is described, and its advantages over current strategies of mass drug administration and vaccination for STH control are highlighted.

Soil-transmitted helminths (STH) are a group of parasitic nematodes of humans that share a common transmission mechanism involving contact with the infective stage in fecally polluted soil. Also known as soil-transmitted nematodes (STN) or geohelminths, the STHs are comprised of the large roundworm *Ascaris lumbricoides*, the hookworms *Necator americanus* and *Ancylostoma duodenale*, and the whipworm *Trichuris trichiura*. A fourth STH species, the threadworm *Strongyloides stercoralis*, is often omitted from the group because of difficulties with detection and treatment. Found throughout the tropics and subtropics wherever poverty and poor sanitation occur, over 1 billion people are infected with 1 or more STH species, and more than 4 billion are at risk of infection (de Silva et al., 2003; Bethony et al., 2006). While low worm burdens often go unnoticed, several groups are particularly susceptible and suffer the majority of the effects. Over 450 million, mostly children, suffer from significant morbidity, and 44 million pregnant women suffer clinical effects from hookworm-associated anemia (Bundy et al., 1995; World Health Oranization [WHO], 1996). The elderly are also recognized as a severely impacted population (Bethony et al., 2002). While rarely fatal, STH infections kill 135,000 people a year. More important are the effects of worm infections on health including anemia, delays in physical growth and cognition, decreased stamina and work output, and complications during pregnancy. STHs cause the loss of 39 million disability-adjusted life years (DALYs) per year—a burden similar to that of malaria or tuberculosis (WHO, 2002; Utzinger and Keiser, 2004; Bethony et al., 2006; Lopez et al., 2006; Brooker, 2010). These infections place considerable drag on the already overburdened economies of developing countries, so there is considerable interest in developing effective control measures.

Safe and effective drugs exist to treat STH infections, and mass drug administration (MDA) has been the approach used toward control and elimination of these infections for the last several decades. Typically, a single anthelmintic dose is administered to school-age children (SAC) either annually or biannually. This "preventative chemotherapy" is designed to decrease individual worm burdens, thereby reducing morbidity. However, elimination or eradication of these parasites is not considered feasible by this approach. In the case of hookworms, vaccine development is currently underway as a means of controlling infection and disease. In this article I will discuss the limitations of current STH control strategies, propose a more sustainable and effective approach for STH control, and suggest how this approach can be adapted for use throughout the world to control, and potentially eradicate, STH infections.

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MASS DRUG ADMINISTRATION FOR PREVENTATIVE CHEMOTHERAPY—AN INADEQUATE STRATEGY FOR STH CONTROL

The effect of hookworms on physical and cognitive development has been long known (Stiles, 1931), but the effects of *A. lumbricoides* and *T. trichiura* on health were more obscure. In the 1990s, several influential papers linked STH infection with detrimental effects on child health and development and suggested that treatment to remove the worms resulted in significant improvement (Pollitt et al., 1991; Nokes et al., 1992; Stephenson et al., 1993; Adams et al., 1994; Nokes and Bundy, 1994). Building on this, the World Health Assembly (WHA) passed a resolution (WHA 54.19) in 2001 calling for the regular treatment of at least 75% of SAC at risk for morbidity from STH infections, with the primary goal of reducing the morbidity associated with heavy STH infections. Simultaneously, integration into existing primary health care systems and establishment of national action plans for STH control were urged to reduce costs and increase the efficiency of MDA (WHO, 2002, 2012b). STH infections were included in the newly defined group of neglected tropical diseases (NTDs). A diverse group of interested parties met in Berlin in 2003 to begin translating this approach into a policy that could be implemented to improve the health of poor populations. From 2003 through 2007, the framework for attacking NTDs was developed; it included integrated control of STH and several other NTDs, namely schistosomiasis, lymphatic filariasis (LF), and onchocerciasis.

The "preventative chemotherapy" strategy to control morbidity from STH infections was further developed in a 2006 manual subsequently published by the World Health Organization (WHO, 2006). Morbidity control for STH infections was defined as the elimination of high and moderate intensity infections by

periodic administration of a single, 400-mg dose of albendazole (ABZ) or a 500-mg dose of mebendazole (MBZ) to high risk populations. These populations were primarily pre-school age children (PAC), 1- to 4-yr-old and SAC, 5- to 14-yr-old, but also included women of reproductive age, pregnant (final 2 trimesters) and lactating women, and specific adult groups at high risk for STH infection. The treatment schedule is once or twice yearly, depending on the initial prevalence of any STH, with the aim of reducing and maintaining low infection levels. In the absence of improved sanitation, which was deemed beyond the resources of developing countries, this strategy is seen as the best short- to medium-term method to control morbidity from STH (WHO, 2012b). To increase efficiency and decrease costs, MDA programs were designed to take advantage of existing public health activities and infrastructure. SAC are treated in schools, where teachers can administer the medication with minimal training while incorporating health education into their curricula. PAC can be dewormed during childhood vaccination campaigns to take advantage of skilled health professionals to administer the drugs. Women of childbearing age can be dewormed when seeking maternal and child health services. Integration of control efforts was also addressed by the concept of "rapid impact packages" of low-cost or donated drugs to treat NTDs endemic to specific regions. These strategies, together with integration of STH control into existing, or ongoing, NTD control programs were expected to allow the ambitious targets established by the WHA to be met.

In 2007, the WHO released a "Plan to Combat NTDs 2008–2015" (WHO, 2007) to intensify efforts toward NTD control. This plan was later expanded in the First WHO Report on Neglected Tropical Diseases (WHO, 2010) and was followed by a "roadmap" in 2012 to guide the implementation of the policies and strategies established in these documents (WHO, 2012a). At a 2012 meeting of the global health community with several pharmaceutical companies, a new public–private partnership was established to eliminate or control NTDs using the WHO roadmap as a guide. This was made more feasible by the commitment in 2010 of several pharmaceutical companies to sustain and expand their donations of ABZ and MBZ (Addiss, 2013). That commitment will make available nearly 5 billion doses by 2020 for preventative chemotherapy of STH infections.

The ambitious goal of treating 75% of the SAC at risk from STH infections by 2010 laid out in WHA 54.19 was not met, with less than a third of the targeted population receiving treatment (WHO, 2012c). Therefore, the WHO amended their global strategy to set a new target of 2020 for eliminating STH as a public health problem and issued a strategic plan to guide governments and public health officials in endemic countries, as well as donors and other interested parties, in implementation of the new strategy (WHO, 2012b).

PROBLEMS WITH MDA

Optimism for STH control

Poor implementation rates, drug costs, and the magnitude of the problem were suggested as explanations for the slow progress toward meeting this goal throughout the first decade (WHO, 2008, 2012a). However, there was optimism in 2010 when the pharmaceutical companies Johnson & Johnson and Glaxo-SmithKline pledged to donate 200 million and 400 million doses of MBZ and ABZ, respectively, over the upcoming decade (Addiss, 2013). These donations, together with a new 10-yr plan, have generated considerable optimism in the deworming community, despite setbacks in reaching the 2010 treatment coverage goals. However, this optimism may be misplaced, as there are several serious limitations to the strategy of preventative chemotherapy by MDA that are conveniently overlooked or downplayed by members of the deworming community. These problems will jeopardize the goal of eliminating the public health consequences of STH infection by 2020 and delay implementation of more-effective and sustainable control methods.

The problem of imperfect drugs

The idea behind preventative chemotherapy is to use an inexpensive, easily administered, and safe anthelmintic to decrease the worm burden below the threshold number that causes clinical pathology and morbidity. The WHO recommends 4 drugs for STH MDA programs. The benzimidazole (BZ) drugs, ABZ and MBZ, are used most frequently, with levamisole (LEV) and pyrantel pamoate (PYR) reserved for special situations (WHO, 2012b). ABZ is typically administered in a single, 400-mg dose whereas MBZ is given as a single, 500-mg dose. The intention has never been therapeutic cure of the infections. However, these drugs exhibit variable efficacy against the individual nematode species and can leave a significant number of worms surviving after a single treatment. A meta-analysis of 20 randomized and placebo-enrolled deworming studies showed that none of the recommended drugs exhibited cure rates (CR) greater than 90% for all 3 species of STH when given as a single dose (Keiser and Utzinger, 2008). All of the drugs have overall CR greater than 89% for *A. lumbricoides*, and the most commonly used for MDA programs, AZ and MBZ, had overall cure rates of 93.9 and 96.5%, respectively, in this study. Efficacy against hookworm was somewhat lower, with overall cure rates of 78.4% for ABZ and 22.9% for MBZ. However, neither drug is particularly effective against *T. trichiura*. The overall CR against *T. trichiura* was 43.6% for ABZ and 23% for MBZ. Perhaps more striking is the relative risk of remaining infected following a single dose of anthelmintic (Keiser and Utzinger, 2008). In the case of *A. lumbricoides*, the combined relative risk after a single ABZ treatment was 0.12, meaning that the risk of remaining infected following treatment was 12%. Put a different way, ABZ has an 88% chance of eliminating an *A. lumbricoides* infection. This is contrasted with hookworm with a pooled relative risk of 0.28 and *T. trichiura* with a combined relative risk of 0.72, indicating that an individual has a 28% chance of remaining infected with hookworm and a 72% chance of remaining infected with *T. trichiura* following a single dose of ABZ. These data indicate that after a single round of MDA, a significant number of worms will remain in the treated population, where they will continue contributing to morbidity and parasite transmission.

Many factors can affect the efficacy of anthelmintics used for MDA including differences in MDA treatment protocols, source of the anthelmintic, and differences in monitoring efficacy. To address these points, a 7-country assessment of the efficacy of a single dose of ABZ against STH infection was commenced (Vercruysse, Behnke et al., 2011). Efficacy was assessed using CR and fecal egg count reduction (FECR), which measures the decrease in the number of eggs released following treatment. This

measure provides a better estimate of the potential effect of treatment on morbidity, as egg count roughly correlates with worm burden (Keiser and Utzinger, 2008). The study found that CR varied by location, age class, and pretreatment intensity. As seen previously, a single dose of ABZ was most effective against *A. lumbricoides* (CR of 98.2%) followed by hookworm (87.8%) and *T. trichiura* (46.6%) (Vercruysse, Behnke, et al., 2011). FECR was generally high (>90%) for *A. lumbricoides* and hookworm, but there was variation across trials and by pretreatment egg count, especially for *T. trichiura*. The authors proposed minimum FECR rate thresholds of >95% for *A. lumbricoides* and >90% for hookworms, anything below which should raise concerns about efficacy. The low efficacy of ABZ and variable FECR rates precluded a recommendation for *T. trichiura* infections. These results suggest that even with standardized protocols and a high quality drug source, single dose ABZ treatment fails to remove the entire worm infrapopulation, which thus ensures continued infection and subsequent reinfection, thereby necessitating return visits. Furthermore, MBZ is a vastly inferior drug, especially against hookworm and *T. trichiura* infections, greatly diminishing the impact of recent large donations. Clearly, the currently available drugs are of insufficient efficacy for the global control of STH infections.

The problem of reinfection

One of the major drawbacks of preventative chemotherapy through MDA is the lack of a strategy to prevent reworming of treated individuals. Transmission of STH occurs in areas with poor sanitation and, frequently, open defecation. Contact with the skin-penetrating infective larvae of hookworms, or ingestion of long-lived embryonated eggs for *Ascaris* and *Trichuris*, results in infection. Furthermore, protective immunity fails to develop against any of the species. Hence, when people return to the same behaviors in the same polluted environment following deworming, they are rapidly reinfected (Schad and Anderson, 1985; Quinnell et al., 1993; Reynoldson et al., 1997). A recent meta-analysis of reinfection studies shows that this reworming happens rapidly in endemic areas, with the prevalence of *Ascaris* and *Trichuris* returning nearly to the initial pretreatment level and that of hookworm to more than half the initial prevalence within 12 mo (Jia et al., 2012). The result is that deworming needs to be done at least annually, and often twice a year, to reduce morbidity even when the initial prevalence of STH infection is as low as 10% (Jia et al., 2012). This is well below the WHO recommendation for biannual deworming (>50% prevalence) and even lower than the prevalence for annual treatment (>20%) (WHO, 2006). Furthermore, deworming targeted against SAC fails to kill a sufficient number of the total worm infrapopulations, especially in the case of hookworm, to significantly impact transmission, thereby ensuring abundant infectious stages available for reinfection (Addiss, 2013; Anderson et al., 2013). In any case, rapid reworming following MDA necessitates subsequent visits at least yearly to have any hope of controlling morbidity from STH infections.

The problem of resistance

Genetic resistance to BZ anthelmintics is a widespread and serious problem in the livestock industry, where several species of parasitic nematodes have developed complete resistance to this class of drugs. The ease and time frame in which this resistance emerged has raised concern about resistance to ABZ developing in STH. Until the widespread implementation of MDA, no human population had been exposed to anthelmintics at rates similar to those used in livestock parasite control and, consequently, no confirmed cases of resistance in STH have been reported although ABZ resistance alleles have been identified in *Wuchereria bancrofti* populations undergoing MDA (Schwab et al., 2005). Additionally, there are reports of high failure rates for MBZ (De Clercq et al., 1997; Albonico et al., 2003; Flohr et al., 2007) and ABZ (Scherrer et al., 2009; Humphries et al., 2011) against human hookworms. With increasing use in MDA programs, selective pressure on human nematode populations will increase to unprecedented levels and will almost certainly lead to genetic resistance emerging in STH populations. The remaining questions are at what rate resistance will emerge and can it be delayed to protect ABZ as a first-line treatment for STH infection.

The threat of emerging ABZ resistance will require monitoring for its appearance in populations undergoing MDA (Albonico, Engels et al., 2004). There are numerous in vitro tests to assess drug resistance that are used in veterinary parasitology, some of which could be adapted for use in monitoring programs for resistance in STH (Vercruysse, Albonico et al., 2011). Also, guidelines for monitoring efficacy were established by the WHO (WHO, 1999) that outlined sampling and counting techniques, frequency, number of subjects, infection intensity, and thresholds defining reduced efficacy. However, these guidelines are in need of updating given the new data generated since their publication (Vercruysse, Albonico et al., 2011). Also, monitoring costs will need to be considered and included in the overall cost of MDA programs. For example, using recent estimates (Speich et al., 2010), the cost of sampling according to the WHO guidelines would be nearly $3.50 per person, or minimally $1,000 per village (Vercruysse, Albonico et al., 2011). All costs are in U.S. dollars unless otherwise stated.

The mechanism of BZ resistance in STH is unknown. In livestock parasitic nematodes, resistance is mediated by several mutations in isotype 1 of the β-tubulin gene, especially the phenylalanine to tyrosine mutation in codons 167 and 200 (Vercruysse, Albonico et al., 2011). However, these mutations were not detected in hookworms recovered from children on Pemba Island, Zanzibar that showed a reduced response to MBZ following 13 rounds of treatment (Albonico, Wright et al., 2004; Schwenkenbecher et al., 2007). Sampling from several countries found a low frequency of homozygous resistance only at codon 200 in hookworms from Kenya (Diawara et al., 2013). The allele frequency did not change in response to ABZ treatment. The codon 200-resistance allele was present in *T. trichiura* from Haiti, Kenya, and Panama. Furthermore, there was a significant increase in the resistant allele frequency after treatment with ABZ. Together with a previous study (Diawara et al., 2009), this indicated that the resistance allele was already present in these *T. trichiura* populations and may explain the poor efficacy of ABZ against this nematode. However, the role of several other tubulin polymorphisms found in the β-tubulin genes of these populations is unclear. Also, the "resistant" genotype at codon 167 was found at high frequency (97.7%) in *A. lumbricoides* in Haiti and Kenya, but the worms were highly susceptible to ABZ treatment, suggesting that this polymorphism does not affect drug efficacy (Diawara et al., 2013). These data clearly indicate that polymorphisms associated with BZ resistance in livestock parasitic

nematodes do not necessarily correlate with resistance in the STHs and that considerably more information about the mechanism of resistance is required before a monitoring program using molecular diagnostics can be implemented. The high failure rates and increasingly diminished efficacy of MBZ will soon mean that the entire success of MDA programs will rest with ABZ. This is a precarious position to be in, given the rapid emergence of resistance to this class of drugs that was seen in nematodes infecting livestock, and it will make monitoring programs absolutely critical to the control of STH infections by MDA. No such program has yet to be developed or implemented.

The problem of cost and sustainability

The low cost of deworming an individual child is often given as a major advantage of preventative chemotherapy. Various costs have been quoted, ranging from US$0.03 to $0.17 per child for STH treatment and $0.79 per child for "rapid impact packages" that treat multiple NTDs (Hotez et al., 2007; Montresor et al., 2007; Phommasack et al., 2008). Integration of STH and other disease control programs (typically lymphatic filariasis) is projected to reduce the per person cost even further, due primarily to the availability of donated ABZ (which is currently only donated for LF control) (Brady et al., 2006; Hotez, 2009). However, the derivation of these financial estimates is rarely transparent and often does not account for drug acquisition or economic costs. A thorough study of the cost of an integrated helminth control program in Haiti was recently reported (Goldman et al., 2011). In 2008–2009, the Haitian national NTD program, Projet des Maladies Tropicales Negligées (MTN), treated all non-pregnant people in nearly half of STH-endemic communes once per year. Nine of the 55 treated communes were randomly selected for a detailed cost analysis that included personnel, per diem, transportation, equipment, anthelmintics, and recurrent operating costs. The study included 663,261 people who were treated in the 9 communes at a cost of $264,970, excluding the price of donated ABZ. Subtracting the cost of diethylcarbamazine (DEC) used to treat LF ($15,274), the outlay of MDA for STH control alone was $0.38 per person. If the charge for ABZ is included, the estimated price for MDA was $387,726, or $0.61 per person. These expenses, whose calculation was more comprehensive and therefore more likely to represent the true cost of MDA programs, are significantly higher than the estimates included above. However, the rates fell dramatically from the $1.30 per person incurred in an MDA demonstration project in Haiti in 2002 (Goldman et al., 2011).

An estimated 2,907,497 people were eligible for deworming in the 55 Haitian communes in 2008–2009, of which 2,890,719 were treated (Goldman et al., 2011). This high coverage rate (85%) was achieved because of the presence of 3 implementing organizations that actively administered drugs. The total dollars to treat 85% of the eligible population was projected to be $1,214,102 or $1,850,153 if the cost of ABZ and DEC are included. While at first glance the ability to deworm 85% of the eligible population for $0.38 seems promising, projection of these costs to larger populations on a national or global scale quickly illuminates 1 of the biggest impediments to MDA as a control strategy. For example, to treat the entire 134 STH endemic communes in Haiti just once, with a population of 8,145,069 it would require from $3,095,126 to $4,968,492 depending on how much of the drug was donated. Assuming complete coverage is even possible, it would need to be repeated yearly for many years to effectively control morbidity. Expanded to a global scale, to treat the estimated 882.5 million children who would benefit from treatment (WHO, 2012b) would cost between $335,350,000 and $538,325,000 per year. Using a significantly more optimistic number of $72,000 to treat 1 million children (Montresor et al., 2010), the cost would exceed $63.5 million per year. Assuming that the treatment of over 800 million children every year is logistically possible, it is difficult to imagine the necessary funds being sustainable for the time required to eliminate morbidity or eradicate STH infection, especially given the rapid reworming that occurs in endemic areas.

An example of the magnitude of effort required to eliminate morbidity from STH in a population can be found in a recent 5-yr-study investigating the effect on anemia of iron and folic acid supplementation, coupled with periodic deworming, in a rural population of Vietnamese women (Casey et al., 2013). The area had a high initial prevalence of hookworm infection (76%). Patients were treated with a single dose of ABZ every 4 mo for the first year and then twice yearly for the remaining 4 yr. They also received iron and folic acid supplementation. At the end of the 5 yr, the prevalence of moderate or heavy intensity infections with any STH had fallen below 1%, the level at which the WHO considers morbidity eliminated, and iron deficiency and iron deficiency anemia were improved. However, the overall prevalence of hookworm remained above 10% after 5 yr. While morbidity was considered eliminated, this required 5 yr of intensive deworming, including a treatment frequency greater than that recommended for MDA programs in a small cohort of infected people who also received nutritional supplementation. To achieve this level at a national or global scale with standard treatment regimens would likely require much more than 5 yr (Hotez et al., 2013). Multiple treatment visits each year for 5 yr or more to all at-risk populations on a global scale would be logistically problematic and most likely unsustainable.

Sustainability is a major concern for MDA programs. As outlined above, the low per person cost of MDA programs is deceptive. One may hear statements like, "For the price of a fancy coffee, 5 people can be dewormed." However, when the number of infected people and the need for repeat visits over many years are factored in, the enormous cost of sustaining control programs becomes starkly clear. Consequently, MDA programs inevitably fail to live up to their promise and are less effective than their proponents originally planned (Smits, 2009). Coverage goals are difficult to reach, as demonstrated by the failure to deworm even a third of those targeted by the World Health Assembly resolution WHA 54.19 (WHO, 2012b). Furthermore, there is considerable debate about the wisdom of concentrating on medical interventions like new drugs and MDA programs that are designed to deworm infected people without programs to prevent reworming of the same people (Singer and de Castro, 2007; Spiegel et al., 2010). Disease-specific, vertical funding is suggested to be counterproductive in that it draws funding away from preventative approaches of strong public health systems of proven effectiveness (Spiegel et al., 2010).

The problem of effectiveness

As morbidity is directly related to the number of worms harbored by a patient, an underlying assumption is that

decreasing this worm burden will decrease clinical morbidity and, consequently, improve health. Indeed, this is the rationale behind preventative chemotherapy by MDA (WHO, 2006, 2012b). This idea is widespread in the deworming community and generally taken to be true (Bethony et al., 2006; Hotez, 2009; Humphries et al., 2012). The often-cited benefits of MDA include improved growth, nutrition, and educational performance as well as economic benefits (Stephenson et al., 1993; Adams et al., 1994; Stephenson et al., 2000; Bethony et al., 2006). According to the WHO, deworming leads to improvements in cognition and intellectual development that have significant effects on income later in life, thereby allowing people to earn enough to escape poverty (WHO, 2005; Hawkes, 2013). Furthermore, the cost-effectiveness of deworming is often highlighted as a major advantage of preventative chemotherapy by MDA. The Copenhagen Consensus, a meeting of influential economists, lists deworming among the top 4 cost-effective interventions along with treating malaria, improved nutrition, and improved childhood immunizations (Copenhagen Consensus Center, 2012; Hawkes, 2013). The Disease Control Priorities in Developing Countries (DCP2), a report published by the World Bank and partially funded by the Gates Foundation, provided an estimate of $3.41 per DALY prevented for the cost-effectiveness of MDA for STH treatment, which would rank MDA as 1 of the most cost-effective interventions for improving global health (Hotez et al., 2006; Alexander, 2011). However, analysis by the organization GiveWell of the spreadsheet used to make the calculation identified 5 errors, subsequently acknowledged by DPC2, that shifted the cost estimate to $326.43 per DALY prevented (Alexander, 2011). GiveWell's own calculation was somewhat lower, at $82.54 per DALY prevented, but was still significantly higher than the original DPC2 estimate. Unfortunately, the inaccurate figure was used widely as justification for increased attention to STH infections and MDA expansion by non-government organizations (NGOs) and academics (Laxminarayan et al., 2006; Hotez, 2007; Liese and Schubert, 2009; Alexander, 2011).

While not as optimistic as originally estimated, $82 to avert a DALY and lift a child from poverty seems like a good investment. As such, considerable public and private funds have been invested in MDA programs (Hotez, 2011) with the assumption that they will improve child health and reduce poverty. If deworming results in improvements in these areas, then the expense of MDA programs might be justifiable. However, there is serious concern whether MDA actually improves the health and performance of infected people. Recent reviews question the dogma that single dose yearly deworming has a meaningful effect on weight gain, cognitive function, school performance, or maternal health. A review by the Cochrane group, first published in 1997 and updated several times since, most recently in 2012, examined 42 deworming trials (Taylor-Robinson et al., 2012). To meet the rigorous criteria for inclusion in the analysis, the studies must be randomized control trials (RCT) that compare deworming drugs with placebo or no treatment in children ages 16 or under and reported data on weight, hemoglobin status, intellectual development, school attendance, and school performance. The trials were performed in 23 different countries. The authors found that screening and treating infected children once may increase weight and hemoglobin, although the small sample size (3 trials) made confidence low. An effect on school performance could not be demonstrated, nor did multiple treatments following screening have any demonstrable effect on any of these measures. When they examined trials in which a single deworming dose was given to all children, which is the strategy advocated by the WHO, the evidence was equivocal. Only 2 of 9 trials showed a positive effect on weight, and these were both from the same high prevalence area in Kenya (Stephenson et al., 1989, 1993). In moderate and low prevalence areas, no clear effect was seen (Taylor-Robinson et al., 2012). No effect was detected for hemoglobin or cognition, although there was some improvement in physical well being (measured by the Harvard step test) at the high prevalence sites in Kenya. Multiple doses given to all school children also failed to have positive effects in any of the measured outcomes including weight, height, hemoglobin, cognitive performance, school attendance, or school performance. They concluded that research has failed to demonstrate that MDA improves physical or cognitive performance and that there is insufficient evidence to justify deworming on the basis of effects on school performance or attendance (Taylor-Robinson et al., 2012; Hawkes, 2013).

Another at-risk group for STH infection, especially hookworms, is women of reproductive age who are particularly susceptible to iron deficiency anemia because of iron loss during menstruation and increased iron requirements during pregnancy (Pawlowski et al., 1991; Bundy et al., 1995). This is a direct consequence of the blood loss associated with hookworms feeding in the small intestine. These women are often borderline or slightly anemic, so the added burden of hookworm infection can tip the balance into frank iron deficiency anemia, resulting in poor fetal and maternal outcomes (WHO, 2001). Therefore, this group is often included as a target population in MDA programs (WHO, 2006). However, the value of a single dose of anthelmintic on maternal and neonate health has also been recently questioned. A Cochrane review of 3 randomized trials in which pregnant woman were given a single treatment in the second trimester found that treatment had no clear effect on maternal anemia, low birth weight, perinatal deaths, or preterm births (Haider et al., 2009; Elliott et al., 2011). In fact, maternal ABZ treatment was associated with an increased risk of infant eczema in 1 study (Mpairwe et al., 2011). The limited number of trials suggests the need for more research to determine if treatment of STH infection during pregnancy is warranted, given the potential risks.

Is MDA the way? CERTAINLY NOT!

Hundreds of pages of advocacy for MDA have been generated by the WHO and its academic partners, and numerous organizations from NGOs and nonprofits to universities and governments have bought into MDA as a feasible solution to controlling STH infection, with at best passing lip service to more-sustainable long-term solutions. Much of this advocacy is based on exaggerations of MDA benefits or lacks rigorous scientific evidence of the effectiveness of preventative chemotherapy (Taylor-Robinson et al., 2012), often actively ignoring evidence-based policy (Nagpal et al., 2013). Drug companies have pledged to donate large quantities of drugs (Addiss, 2013), likely as much for philanthropic reasons as to generate positive corporate images. Academics who have built their careers on the idea that deworming is a viable solution vigorously defend their positions when deficiencies in this strategy are highlighted (Anonymous,

2012; PLoS Medicine, 2012; Bundy et al., 2013; Montresor et al., 2013). Celebrities have signed on to persuade the public to forgo some daily indulgence or luxury item to help deworm poor children, for what amounts to a worm-free year at best, without serious consideration of why they are infected. Even modest gains in health might be worth pursuing, and seeking any improvement in child health is certainly a noble cause. However, preventative chemotherapy must be recognized as a stop-gap solution, only to be done while long-term, sustainable solutions are implemented and not as an ongoing or permanent solution to STH infection. Little has been done to implement a long-term strategy, wasting precious time and resources on an ultimately unsustainable fix to an eminently solvable problem.

WHY VACCINES CANNOT CONTROL STH

Vaccines for STHs?

Prevention of infection by vaccination has been an unqualified success in reducing or eliminating some of humanity's most important infectious diseases. It is not hyperbole to say that vaccines are one of the major drivers behind the success of Western healthcare systems. Their success in reducing morbidity and mortality from viral and bacterial infections makes development of vaccines against diseases caused by eukaryotes highly desirable. However, these organisms, with their complex life cycles, large size, and sophisticated immune-avoidance mechanisms, present far more-difficult targets for vaccination, as demonstrated by the lack of any marketed vaccine against a human protozoan or helminth infection. An effective recombinant vaccine against STH infections, if sufficiently efficacious, would represent a powerful tool to reduce morbidity and perhaps lead to elimination or eradication. However, development of such a vaccine is an enormous undertaking and, until recently, unthinkable due to the huge development cost and small commercial market for the product. The entry of the Gates Foundation into the NTD field has led to establishment of the Human Hookworm Vaccine Initiative (HHVI) with the goal of developing a recombinant anti-hookworm disease vaccine (Hotez et al., 2003). This is the only extant vaccine program for an STH infection, and its history, promise, and problems are discussed below.

History of hookworm vaccines

In the 1960s, Miller successfully vaccinated dogs against challenge infection using irradiated *Ancylostoma caninum* L3 (irL3) (Miller, 1964, 1971). This vaccine reduced infectivity, blood loss, and fecundity of hookworms in vaccinated hosts but failed to induce a sterilizing immunity. Miller argued that a sterilizing immunity would be impossible against a large, multicellular nematode and that it was not necessary, as hookworm disease severity is directly related to the worm burden (Miller, 1971; Schneider et al., 2011). The vaccine lowered the number of worms that established in the host and, therefore, prevented disease but not infection. The vaccine was developed, field tested, and marketed commercially for a short time. However, the difference between infection and disease was a hard sell for veterinarians and their clients, who expected a vaccinated dog to be egg-free on a fecal exam (Miller, 1978). This, together with special storage requirements and a short shelf life, led to its withdrawal from the market in 1975 (Schneider et al., 2011). Despite commercial failure of the irL3 vaccine, Miller continued to advocate for the difference between hookworm infection and disease. The idea that a vaccine against hookworm could protect against disease by limiting the number of blood-feeding adults without the necessity of generating a sterilizing immunity was adopted by later hookworm vaccine researchers and is the goal of current hookworm vaccine efforts of the HHVI (Hotez et al., 2003).

The HHVI was established based on work done in the 1990s that identified the first larval candidate antigens from hookworms. The breakthrough came with the development of an in vitro system in which infective L3 of *A. caninum* were induced to feed, or "activate," by incubation with serum components and glutathione (Hawdon and Schad, 1990, 1992). In addition to resuming feeding, activated L3 also released 50–100 excretory–secretory proteins (ESP) into the incubation media (Fig. 1). Activation is thought to be an early step in infection, and these secreted proteins are likely the first molecules to interact with the host, suggesting a role in establishing the host–parasitic association (Hawdon and Schad, 1991; Hawdon and Hotez, 1996). The timing of their release and their likely involvement in infection made them excellent candidate antigens for a hookworm vaccine. The amino acid sequence of the most abundant protein in the activated L3 ESP was determined and used to clone the cDNA encoding a member of a large family of CAP (cysteine-rich secreted proteins (CRISPs)/Antigen 5/Pr-1) proteins found in numerous taxa (Hawdon et al., 1996). The protein, named *Ancylostoma* secreted protein-1 (ASP-1), contained 2 similar domains and was most closely related to the antigen 5 protein from the venom of the fire ant, *Solenopsis invicta* (Hoffman, 1993). This protein is among the most allergenic proteins in the venom of hymenopterans and causes many of the allergic reactions associated with stings. A second, single-domain protein related to ASP-1 was subsequently isolated from ESP and named ASP-2 (Hawdon et al., 1999). Other members of the ASP/CAP family were later identified in hookworms and other nematodes (Zhan et al., 1999; Cantacessi et al., 2009).

Initial vaccine studies were performed in a non-permissive mouse model in which L3 would migrate through the lungs but fail to establish in the intestine. When ASP-1 vaccinated mice were challenged with *A. caninum* L3, the number of L3s recovered from the lungs at 48 hr post-infection was significantly decreased (79% reduction) compared to unvaccinated controls (Ghosh et al., 1996). While intriguing, the mechanism of inhibition was unknown and the results difficult to interpret in a non-permissive host. Nevertheless, these data were the basis of a successful solicitation to the Gates Foundation for funding to develop a recombinant hookworm vaccine. A product development partnership (PDP) was established in 2000 with an $18 million grant to the Sabin Vaccine Institute (SVI) to target *N. americanus* infections (Hotez et al., 2013).

ASP-1 was among the first vaccine antigens tested, but performed poorly in challenge trials in the hookworm-permissive *Ancylostoma ceylanicum*–hamster model, so ASP-2 was advanced as the lead antigen for human trials despite having only marginally better protection (Goud et al., 2004; Bethony et al., 2005; Loukas et al., 2006). A Phase I trial in naïve volunteers in the United States, using *N. americanus* ASP-2 (*Na*-ASP-2) with the adjuvant Alhydrogel, was immunogenic and showed no serious safety concerns (Bethony et al., 2008). A 5-yr, $21.8

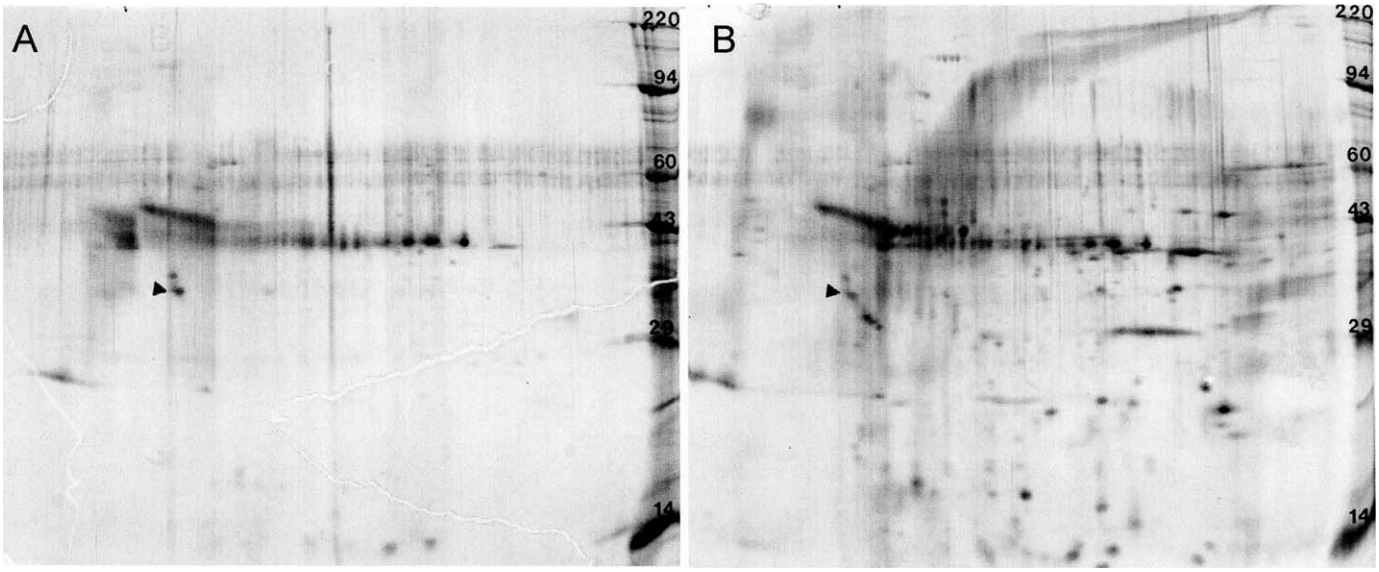

FIGURE 1. Proteins secreted by non-activated (**A**) and activated (**B**) *Ancylostoma caninum* third-stage larvae (L3). Excretory–secretory proteins from approximately 75,000 non-activated and activated L3 were analyzed by 2D gel electrophoresis at Kendrick Labs, Inc. (Madison, Wisconsin) according to the method of O'Farrell (O'Farrell, 1975). The arrowhead points to the internal standard tropomyosin.

million Gates Grant to support clinical development and evaluation of the vaccine followed, and a second Phase I safety trial of the *Na*-ASP-2 vaccine was conducted in a small cohort of adults in a hookworm-endemic region of Brazil (Bethony et al., 2008). This trial was halted when 3 of 7 volunteers (43%) vaccinated with *Na*-ASP-2 developed an acute, severe, generalized urticarial rash on the upper body 1–2 hr after vaccination. Analysis indicated that the reaction was associated with elevated levels of ASP-2–specific IgE in patients that developed the rash, and that significant numbers of people in the region had IgE antibodies against ASP-2 (Diemert et al., 2012). These elevated IgE levels are most likely associated with prior hookworm exposure, confirming that ASP-2 is secreted during infection and generates an immunological response (Hawdon and Hotez, 1996; Hawdon et al., 1999).

The failure of *Na*-ASP-2 as a vaccine candidate led to testing of all candidate antigens for reaction with IgE-specific antibodies as well as to the somewhat hasty abandonment of the strategy to use larval secretory proteins in vaccines (Hotez et al., 2010). Efforts switched to targeting adult antigens, specifically those involved in blood feeding (Schneider et al., 2011). Two antigens have emerged as leads, i.e., a gut aspartyl protease (*Na*-APR-1) and a glutathione S-transferase (*Na*-GST-1). Neutralizing antibodies against enzymes involved in feeding are hypothesized to interfere with blood feeding, thereby starving the parasite to death. *Na*-APR-1 is the first enzyme in a proposed hemoglobinase degradation pathway (Williamson et al., 2004; Ranjit et al., 2009), and *Na*-GST-1 is believed to detoxify oxygen radicals generated by free heme released by hemoglobin digestion (Zhan et al., 2005, 2010; Perally et al., 2008). A Phase I trial of *Na*-GST-1 is currently underway in Brazil, and *Na*-APR-1 is under manufacture (Hotez et al., 2013). The eventual goal of the HHVI is to develop a bivalent vaccine containing these 2 adult antigens (Hotez et al., 2013).

Although far from implementation, a target product profile for a Human Hookworm Vaccine has been established (Hotez et al., 2013). The vaccine is intended for children under 10 yr of age in developing countries who are at risk for moderate or heavy hookworm infections. Two doses of the vaccine will be given by intramuscular injection, and it will be designed to be given concurrently with other childhood vaccines to take advantage of distribution networks currently in place. Storage of the vaccine will require refrigeration at 2–8 C. The targeted efficacy is a minimum of 80% in preventing moderate and heavy *N. americanus* infections, and the vaccine must protect for at least 5 yr to be cost effective (Hotez et al., 2013). Economic modeling suggests that even a vaccine of low efficacy could be cost effective at reducing morbidity if used in conjunction with deworming, provided it was at least 30% effective in preventing infection, 40% effective in reducing egg output, and cost less than $100 to fully vaccinate an individual (Lee et al., 2011). Advocates also argue that when coupled with MDA, vaccination can eliminate hookworm in endemic areas (Hotez et al., 2013). Such a vaccine would be a major medical advance. The overarching question is whether one can be developed.

PROBLEMS WITH HOOKWORM VACCINES

The goal

Developing a hookworm vaccine is a laudable goal, and implementation of an efficacious recombinant vaccine in tandem with MDA might accelerate morbidity reduction significantly (Hotez et al., 2013). Considerable progress has been made in establishing a pipeline to bring potential vaccines for neglected diseases, such as hookworm, from the bench to clinical testing in an academic setting, a requirement for the development of vaccines with limited commercial markets (Bottazzi and Brown, 2008). Furthermore, a well-directed antigen discovery strategy and an investigation of the immunological response to hook-

worms in the context of vaccine development should generate useful biological information about the parasite and host interaction. However, several factors inherent in the biology of hookworms, as well as the lack of any basic research component in the program, have led to disappointing results to date. Some of the inherent difficulties and setbacks are outlined below.

The problem of animal models

Perhaps the greatest issue for vaccine development is the lack of an animal model that accurately represents the immunological and clinical aspects of hookworm infection. Animal models currently used for hookworm include natural host–parasite relationships (*A. caninum* and *A. ceylanicum* in canines) and non-natural permissive host–parasite relationships (*A. ceylanicum* and *N. americanus* in hamsters). Both of these hosts are poorly characterized, especially immunologically, so the reagents required for detailed investigation of the immune response to hookworm are unavailable. Canines are large and expensive to purchase and house, as well as culturally sensitive for experimentation, making vaccine trials costly to conduct. Worm burdens, egg counts, and blood loss tend to be highly variable, and none of the model systems mimics the clinical sequelae of human infections accurately (Schneider et al., 2011).

The *N. americanus*–hamster model is especially problematic. Originally, an Indian strain was adapted to Syrian golden hamsters (*Mesocricetus auratus*) through percutaneous infection of neonatal hamsters (Sen and Seth, 1970; Sen, 1972; Sen and Deb, 1973; Behnke et al., 1986; Behnke and Pritchard, 1987). While relatively stable and high worm burdens could be achieved from low larval doses (50–100 L3), the need to infect neonates makes this strain unsuitable for vaccination–challenge experiments. A strain was developed at the Institute for Parasitic Diseases in Shanghai through subcutaneous passage in Chinese hamsters (*Cricetulus griseus)* that can be used for challenge studies, but it also has several serious limitations (Xue, Liu et al., 2003; Xue, Xiao et al., 2003; Xue et al., 2005; Schneider et al., 2011). Establishment of adults in the intestine rarely exceeds 25% of the dose and is highly variable. For example, in 2 vaccine trials, animals were challenged with 250 L3, and the mean number of adults that established in the controls was 11.8 ± 4.6 and 17.1 ± 6.3 (Zhan et al., 2010). Subcutaneous injection bypasses the skin, which may be involved in the immune response to *N. americanus* in both humans and animals. Finally, this strain performs poorly in Syrian golden hamsters and is quickly lost. Moreover, Chinese hamsters are difficult to obtain and use as research animals outside China, making independent replication of challenge experiments impossible.

Perhaps more significant is the considerable debate as to whether the immunology of hookworm infection in any of the animal models mimics that seen in human infections (Fujiwara et al., 2006). Both dogs and hamsters exhibit a natural age-associated resistance to infection, even in their permissive hosts (Miller, 1971; Behnke, 1990). More worrisome, unlike humans who fail to develop a protective immunity despite a vigorous immunological response and multiple infections over their lifetimes (Miller, 1968, 1971; Fujiwara et al., 2006; Schneider et al., 2011), both hosts are resistant to secondary infections (Miller, 1971; Xue et al., 2012). The ability to develop immunity to hookworm infection indicates that the model hosts' immune responses differ significantly from the response of humans, and that the model host can generate a protective immunity to a natural hookworm infection that humans cannot. This leads to questions about the utility of unrepresentative animal models in identifying antigens that will generate a protective response in humans. It is unlikely that humans can mount a protective immune response to a recombinant antigen when a natural infection fails to generate protection. Furthermore, protection in animals cannot reasonably be assumed to translate to similar levels in humans (see below).

The problem of antigens

Three antigens have either made it to clinical trials or are scheduled to be evaluated in trials as potential hookworm vaccines. In all cases, the molecules advanced to clinical trials based on the results of vaccination–challenge trials in 1, or more, of the problematic animal models above. *Na*-ASP-2 was tested in the 3 hookworm model systems, where it showed limited reduction in worm burden in challenge infections. In canines, vaccination with *Ac*-ASP-2 caused a 69% reduction in egg counts but only a 26% reduction in worm burden (Bethony et al., 2005). Vaccination of hamsters with the *A. ceylanicum* ortholog, *Ace*-ASP-2, reduced the worm burden by 32% in challenge experiments (Goud et al., 2004; Mendez et al., 2005), and *Na*-ASP-2 performed similarly in several challenge studies in the hamster–*N. americanus* model (30–40% reduction) (Xiao et al., 2008). Despite these marginal protection levels, *Na*-ASP-2 underwent Phase 1 safety testing and, while found to be safe in naïve patients, elicited a hypersensitivity reaction in more than a third of human recipients in a hookworm-endemic region of Brazil (Diemert et al., 2012).

After the clinical failure of the *Na*-ASP-2 vaccine, the HHVI switched from a mixed larval–adult antigen vaccine to a bivalent adult antigen vaccine strategy. *Ac*-GST-1 was tested in both the *A. caninum*–dog and *N. americanus*–hamster models for protection against challenge (Zhan et al., 2005). In dogs, *Ac*-GST-1 vaccination caused a 39.4% reduction in *A. caninum* worm burden whereas in hamsters *N. americanus* worm burden was decreased by 57.3%, a somewhat surprising result for a heterologous antigen. A second trial using *Na*-GST-1 in hamsters showed a more typical 30–40% worm burden reduction in several challenge infection trials (Zhan et al., 2010). The aspartyl protease *Ac*-APR-1 was first tested as a vaccine in canines, where it reduced overall worm burden by 33%, which was not significant ($P = 0.095$) (Loukas et al., 2005). There was a difference in the effect between sexes, with a 30% reduction in males and a 40% reduction in females, neither of which was statistically significant. The larger decrease in females probably accounts for the overall decreased egg output in vaccinated dogs. There was also a slight protective effect of vaccination on anemia, but the difference was not significant. Next, *Ac*-APR-1 was tested in the problematic Chinese hamster–*N. americanus* vaccine model (Xiao et al., 2008). Vaccinated hamsters had a 44% reduction in worm burden, similar to that seen with *Na*-ASP-2 and *Ac*-GST-1. Finally, an enzymatically inactivated *N. americanus* ortholog of APR-1 was tested in the heterologous *A. caninum*–dog vaccine model (Pearson et al., 2009). Like several other hookworm vaccine antigens, *Na*-APR-1_{mut} induced a strong IgG antibody response and also resulted in significant improvements in weight gain and

reduced egg output. However, the 26% reduction in worm burden in vaccinated dogs was not statistically significant nor was there any effect on hemoglobin levels of vaccinated dogs (Pearson et al., 2009). The authors point out that this was a heterologous vaccination–challenge regime and that protection obtained in this model is likely to be higher in a homologous scenario (Pearson et al., 2009). However, this was not seen in previous vaccine trials from this group, where heterologous antigens protected at similar or even higher levels (Zhan et al., 2005, 2010).

Impaired hemoglobin digestion and nutrient acquisition by APR-1 neutralizing antibodies was proposed as a mechanism for the decreased fecundity in *Na*-APR-1 vaccinated dogs (Pearson et al., 2009). However, the effect of this reduced fecundity on the clinical aspects of hookworm infection and health are likely minor. There was no effect on worm burden or hemoglobin levels in vaccinated animals. While the investigators attempt to elevate the importance of reduced fecal egg counts in response to vaccination, reduced fecundity in the worms will do little to improve the health of vaccinated people, and would be unlikely to affect transmission, as the percentage of hookworm egg output from infected children (the vaccine target group) in the population is estimated to be as low as 15% (Anderson et al., 2013).

Clearly then, the only useful measures of protection are those that would have a direct effect on hookworm disease, namely reduction in worm burden or anemia. Unfortunately, none of the "successful" antigens reduced worm burden by more than 40%. Given the unrepresentative nature of the animal models, it seems overly optimistic to assume that the limited protection levels seen in animals will be reached in humans. Furthermore, the likelihood of reaching the targeted efficacy of at least 80% in preventing moderate and heavy *N. americanus* infections (Hotez et al., 2013) would appear to be low. Nevertheless, despite little or no evidence of protection in animal models, *Na*-GST-1 and *Na*-APR-1 vaccines were advanced for clinical testing. However, the ethical and economic justification of pursuing candidate vaccines that confer only modest protection in suboptimal animal models, in light of the demonstrated risk to human subjects seen in previous trials, has been questioned (Bungiro and Cappello, 2011). An *N. americanus* challenge model is currently under development for testing vaccine antigens for protection in humans, which would provide relevant information early in clinical development about the true protective ability of a potential vaccine prior to subjecting large populations in hookworm endemic areas to costly and time-consuming Phase 2 and 3 clinical trials (Hotez et al., 2013).

Other concerns

A recent review highlighted the challenges and potential benefits of a hookworm vaccine, including cost effectiveness, the potential for a rapid fall in DALYs, and even possible elimination of hookworm from endemic areas when the vaccine is coupled with MDA (Hotez et al., 2013). Careful examination of the claims for such far-reaching effects of a hookworm vaccine raises several concerns. First, all projections and predictions are dependent on the vaccine meeting the proposed product target profile, which may prove difficult or impossible. Protection levels in animal models have been unspectacular at best, and there is no reason to assume they will be any higher in humans. Hence, reaching a target efficacy of 80% seems overly optimistic. Additionally, the number of doses that would be required is unknown, and protection for 5, or more, years cannot be assumed. The only anti-nematode vaccine available today is a partially protective irL3 vaccine for the bovine lungworm *Dictyocaulus viviparous*, which fails to generate a lasting immunity and, therefore, must be re-administered yearly in the absence of natural challenge (McKeand, 2000). As hookworm model hosts either become resistant with age or immune following infection, and essentially no protective immunity is generated in a natural infection in humans, there is little evidence to suggest that long-term immunity will develop following vaccination.

Perhaps more troubling is the suggestion that a hookworm vaccine that protects for at least 5 yr would interrupt hookworm transmission and reduce morbidity in children and adults, leading to elimination of hookworm from endemic areas (Hotez et al., 2013). However, data from an unpublished mathematical model presented in the review indicate that when coupled with MDA, vaccination fails to eliminate hookworm in any age group in 20 yr! Prevalence in children would fall by slightly over half, and in adults by less than a quarter, in 20 yr using a 5-yr-vaccine and annual administration of MDA to 75% of children (Hotez et al., 2013). Also, as both the vaccine and the MDA target children, who account for as little as 15% of total hookworm egg output, this strategy is unlikely to eliminate transmission (Anderson et al., 2013). Presently, there are proven methods available to eliminate hookworms and other STH that would operate on a much more rapid time scale (see below).

There are several other concerns about the development and implementation of a hookworm vaccine. The current effort is directed solely toward a vaccine for *N. americanus*. This species is the most widespread and common species infecting humans, and this has been used as the rationale for targeting it exclusively. However, the other major hookworm, *A. duodenale*, is far more virulent, infects a significant number of people in India, China, and Africa, and is completely ignored in discussions of a hookworm vaccine (Jonker et al., 2012). While some *N. americanus* antigens share high identity with other *Ancylostoma* species (Zhan et al., 1999), cross-protection is not guaranteed. More information about antigen identity will be available with the upcoming release of the *A. duodenale* genome sequence, which will allow sequence comparison of vaccine antigen orthologs of the 2 species. However, cross-protection by a vaccine using an *N. americanus* antigen will require clinical testing in *A. duodenale*-infected people. Similarly, the current hookworm vaccine antigens are derived from a laboratory strain of *N. americanus* originally acquired from infected people in China (Xue et al., 2003). The effect of laboratory passage through multiple generations is unknown, and it is possible that the antigen sequence has diverged significantly from wild hookworm populations through inbreeding or genetic drift. Furthermore, there appears to be significant variation between natural populations of *N. americanus* on a provincial scale in China (Hawdon et al., 2001), raising the distinct possibility of significant genetic differences between *N. americanus* populations globally. The amount of genetic variability at this scale is unknown, but the effect on vaccine efficacy could be significant depending on the amount of antigen sequence variability. A requirement for species- or region-specific vaccines would certainly affect the feasibility of developing and implementing an efficacious hookworm vaccine. Concerns about geographical or species variability in antigen sequence and its

potential impact on efficacy have received little consideration in the vaccine development program.

Another concern that receives little, or no, attention in the design of the hookworm vaccine is its potential effect on hookworm virulence. Mathematical modeling suggests that vaccines that fail to induce sterile immunity, i.e., "imperfect vaccines," can influence the virulence of parasites in populations of vaccinated people (Gandon et al., 2001; Gandon and Day, 2003; Gandon et al., 2003). Vaccines that target growth are predicted to increase virulence in parasites, thereby increasing risk to non-vaccinated people. A hookworm vaccine targeting blood feeding would most likely fall into this category and could be cause for concern. While these models were developed for microparasites, any intervention that leaves a significant fraction of the parasites alive is likely to exert selective pressure on parasites to resist the vaccine or better exploit the host. The effects of an imperfect hookworm vaccine should be modeled prior to deployment to avoid unintended effects on hookworm virulence.

Finally, deworming will need to continue even in the presence of a highly efficacious vaccine. Several groups that suffer high morbidity would be excluded from vaccination, including pregnant and childbearing-age women and the elderly. Furthermore, a hookworm vaccine would have no effect on the other STH infections. While less virulent than hookworm, *A. lumbricoides* and *T. trichiura* infections account for significant morbidity in developing countries. An approach targeting all the neglected STH infections would certainly be more cost-effective and desirable than one neglecting two-thirds of the problem.

A vaccine to save the world?

The effort to develop a hookworm vaccine is a worthwhile cause, and an effective vaccine could alleviate a significant amount of morbidity in the developing world. Ideally, a strategy of basic research to investigate the biology of hookworms and their interaction with the human immune system should have been employed to identify numerous potential vaccine antigens. Promising antigens would undergo testing in animal and human challenge models to determine which confer protection, with the most efficacious advancing to clinical trials. In this way, a pool of vaccine antigens would have been available for sequential testing as others failed. This was not the case. Little of the more than $50 million allocated to date (SVI, 2013) was spent on basic research, but instead was used to move 1 or more antigens into clinical trials as fast as possible. This strategy was dictated by the funding agency, not the researchers, but the end result is that little new information about the biology and immunology of hookworm infection has emerged from the vast sum of money invested to date. Should an effective hookworm vaccine be developed in the near future, this criticism will vanish. However, based on the results in animal models, the current vaccine candidates undergoing testing are unlikely to protect at the overly optimistic level stipulated in the hookworm vaccine product target profile. Lower efficacy will force re-evaluation of the economics of vaccination with a sub-optimal vaccine and its predicted effects on morbidity and transmission (Hotez et al., 2013). Furthermore, evidence of protection by the current vaccine antigens is minimally several years away because they are currently in Phase 1 testing. Should they prove to be protective in these safety trials, it will be at least a decade before a vaccine is tested for efficacy and available for implementation, a process that will add significantly to the already high costs of development. If the vaccine meets the target goals for efficacy and duration, predicted reductions in DALYs and effects on transmission would follow more than 2 additional decades later (Hotez et al., 2013). This means that MDA would be the only available control strategy for the next 30–40 yr, and will still be an integral part of STH control after that, assuming the current drugs are still effective. This seems to be a long wait for a partial solution, during which time morbidity from hookworm infection will continue.

Despite these problems, development of a human hookworm vaccine should continue. A human challenge model will greatly improve testing of candidate vaccines and allow those with a high chance of success to advance through clinical trials. Antigen discovery will be greatly accelerated by the impending release of high quality draft hookworm genomes, and diversion of some money into basic research would further increase the antigen discovery rate. A pipeline for moving vaccines and drugs of neglected diseases through the regulatory pipeline is now established and will speed regulatory approval of new vaccines (Bottazzi and Brown, 2008). However, relying on a vaccine to end morbidity from hookworm infection seems shortsighted and, along with MDA, should be viewed at best as temporary fixes until long-term, sustainable solutions are implemented.

SANITATION: TIME TO THINK INSIDE "THE BOX"?

Safe disposal of human waste through access to and use of sanitary facilities has long been associated with lower STH prevalence and reinfection rates (Henry, 1988; Huttly, 1990; Esrey et al., 1991; Henry et al., 1993; Sorensen et al., 1994; Asaolu et al., 2002; Asaolu and Ofoezie, 2003; Moraes et al., 2004; Barreto et al., 2010; Mascarini-Serra et al., 2010). A recent meta-analysis and review of the effect of sanitation on STH infection found that prevalence decreased with increasing availability and use of sanitary facilities (Ziegelbauer et al., 2012). More profound and sustainable effects are seen with integrated approaches involving treatment and improved water and sanitation (Singer and de Castro, 2007; Utzinger et al., 2009; Bartram and Cairncross, 2010; Mara et al., 2010; Spiegel et al., 2010). Dramatic reductions in prevalence, and eventual eradication, of STH by improved sanitation were seen in the southern United States, Japan, and Korea (Hong et al., 2006; Kobayashi et al., 2006; Humphreys, 2009). Recently, an integrated schistosomiasis control program in China containing a sanitation component has had secondary effects on STH prevalence (Wang et al., 2009). These and other investigations indicate that sanitation, with or without health and hygiene education, reduces the prevalence and intensity of STH infections, and this rate is improved when combined with deworming (Asaolu and Ofoezie, 2003). Overwhelming evidence indicates that sanitation is the best and most sustainable option for STH control and that improved sanitation addresses the underlying causes of many diseases of poverty (Okun, 1988; Esrey et al., 1991; Bartram and Cairncross, 2010).

While adequate sanitation is an ideal long-term solution, there are several obstacles to sanitation as a control strategy for STH infections. In some cases providing, or increasing the number of, latrines fails to significantly affect STH prevalence or intensity (Bradley et al., 1993; Sow et al., 2004). This can be a matter of time, as improved sanitation can take a long period to reduce

prevalence, especially in the absence of concomitant deworming (Bradley et al., 1993; Mascarini-Serra, 2011). However, sanitation and education are more sustainable than deworming because they control infections over longer periods by preventing transmission and can potentially lead to eradication (Asaolu and Ofoezie, 2003). More frequently, the type of latrine or sanitation system and community awareness and engagement determines the overall impact on STH transmission. Poorly maintained latrines, regardless of type, are often abandoned, and lack of spare parts, water supply, or expertise can lead to malfunction and non-use (Asaolu and Ofoezie, 2003). Also, certain types of latrines are more likely to leak waste and contaminate the environment, actually resulting in increased transmission (Asaolu and Ofoezie, 2003; Baker and Ensink, 2012; Ziegelbauer et al., 2012). Furthermore, sanitary facilities must be culturally appropriate to ensure their use (Esrey et al., 1991; Sow et al., 2004).

The number of people with access to latrines, or the coverage rate, is another important factor in the overall impact of sanitary improvements on STH transmission. Advocates for MDA programs cite a latrine coverage rate of greater than 90% in order to have any effects on STH transmission (Albonico et al., 2006) but provide no empirical evidence for this number. Regardless, a high coverage rate is certainly required, as it only takes a few infected individuals defecating indiscriminately to maintain transmission (Okun, 1988). High coverage requires resources that are often unavailable in poor countries, making sanitary improvements difficult to implement. Furthermore, a high coverage rate does not always translate to effects on STH infections. In areas that use human feces, or night soil, as fertilizer, latrine coverage is very high yet has little effect on prevalence or intensity of STH infections (Humphries et al., 1997; Yajima et al., 2009). When night soil is used on crops, people become infected during agricultural activities from infectious stages in feces that are purposely distributed into the environment. In this case, a sanitary option that renders the feces harmless is required. This implies that implementation of sanitary facilities that fail to account for transmission patterns and sources are destined to fail. Therefore, well-designed, culturally sensitive sanitary facilities, designed with an understanding of transmission patterns and that will be used regularly or exclusively, are required to realize the maximum benefit from improvements in sanitation.

Despite acknowledging the need for improvements in sanitation and health education in order to control STH (Albonico et al., 2006; Hotez et al., 2008; Hotez, 2009; Smits, 2009; Spiegel et al., 2010; WHO, 2012a), proponents of vertical, disease-specific intervention programs inevitably fail to consider, let alone incorporate, sanitation in STH control programs. Instead, they typically advocate for new drugs or tweaks to current MDA programs (Sorensen et al., 1994; Humphries et al., 2012). MDA proponents frequently give cost as the roadblock to improving sanitation. However, incorporation of appropriate technology designed to prevent reinfection in drug-based control programs would go a long way toward increasing sustainability, decreasing long-term costs, and ultimately improving the current and future health of millions more people than MDA alone (Singer and de Castro, 2007). Furthermore, these cost estimates invariably fail to account for the positive secondary effects that flow from improved sanitation. By removing the underlying cause of diseases of poverty, sanitation supports economic growth and development (Okun, 1988; Esrey et al., 1991; Albonico et al., 2006; Bartram and Cairncross, 2010). Benefits that are often overlooked are time savings associated with better access to sanitation and the productivity and economic gains due to overall better health and less time spent ill. When such costs are factored in, the cost–benefit ratio of low cost improvements outlined in the Millennium Development Goals ranges from $5 to $36 per $1 invested, depending on region, with a global average of $8:1 (Hutton et al., 2006). Therefore, the overall benefits of sanitation far outweigh those of unsustainable biomedical interventions for the control of STH infections.

Because of the direct interrelationship of sanitation and STH transmission, control efforts that improve sanitation within a culturally acceptable framework represent the ideal, sustainable strategy for short-term control and eventual eradication of STH infections. Improved sanitation would interrupt transmission and lead to sustainable reductions in morbidity caused by STH and other diseases. Sanitary interventions are non-invasive and performed on a group (household or community) level rather than on individuals. An inexpensive, technologically straightforward intervention that reduces or eliminates environmental contamination is required. Below, I propose one such sanitation-based intervention as a method for sustainable STH control and describe how it is currently being implemented.

Biogas: A sanitation-based STH solution for China?

A Western-style sanitation infrastructure, like modern sewage systems, is beyond the resources of both the donor community and the governments of countries plagued by STHs. What is needed instead is a bottom-up, culturally appropriate, economical sanitary technology that can be implemented rapidly, broadly, and inexpensively. While there are many new sanitation technologies available that may meet these requirements, 1 proven method has great potential to make rapid progress toward controlling and eventually eliminating STH infections in the near future. Biogas technology offers economically desirable, bottom-up, community-driven sanitation to control waste for a fraction of the cost of Western-style sanitation infrastructure and at a long-term cost that competes favorably with current top-down, disease-specific approaches such as MDA and vaccines. Furthermore the secondary impacts, including energy generation and benefits to health and the environment, make this simple technology among the most cost-effective public health interventions available for resource-poor countries. In the following sections, I describe biogas technology, discuss its positive effects on health and the environment and, using China as an example, show how biogas technology can be used to combat STH infection in developing countries.

STH burden and transmission in China

STHs represent a significant health burden in China, where the overall number of *Ascaris*, *Trichuris*, and hookworm infections were estimated at 531, 212, and 194 million, respectively (Xu et al., 1995). China accounts for nearly 50% of the more than 1.2 billion global *Ascaris* infections and still has the highest prevalence (de Silva et al., 2003). Despite widespread, intensive deworming programs, the prevalence of STH infections remains stubbornly high. A more recent nationwide survey (2001–2004) revealed a 20% overall prevalence of STH infection in China

(Chen et al., 2008). Transmission of STHs in rural China is associated with the ancient practice of using human feces, or night soil, as fertilizer for dry land crops (Chang, 1949; Ling et al., 1993; Luo, 2001). With rural per capita incomes often less than $800 per year, night soil offers a readily available and inexpensive high quality substitute for commercial fertilizers and is treated as a valuable commodity by Chinese farmers. In 1993, a survey indicated that more than 93% of human excreta was used as fertilizer (Pan et al., 2001) and, while this has certainly decreased since then due to urbanization and other factors, night soil use is still widespread and common in rural China. Typically, human waste is mixed with animal waste and water to form a slurry that is periodically applied to fields and crops as fertilizer. This results in contamination of soil and plants with eggs or infective larvae of STHs, suggesting that the primary mode of STH transmission in rural China occurs in the agricultural fields where farmers come into contact with the infective stages. The prevalence increases among farmers working directly in the fertilized soil surrounding the plants, as opposed to in the nursery beds or in night soil storage pits (Chang, 1949). Composting of night soil with crop residues, if done properly, can kill parasite infective stages, but this step is often not done long enough for effective parasite killing to occur or is skipped entirely. Nearly all rural farmers use night soil on the Chinese mainland, and STH transmission is primarily associated with agriculture, so night soil use is the major contributor to STH infection.

As a key driver of STH transmission in China, the use of night soil and its cultural context provide a unique opportunity to use technological interventions that improve sanitation to control infection. Latrines are typically connected to night soil storage cisterns where human and animal wastes accumulate at the rear of the house. The value and importance of night soil as a fertilizer leads to extremely high latrine coverage and use. For example, at 2 villages in Sichuan Province, we found that every household had a latrine that was used by family members for most defecation (J. Hawdon, unpubl. obs.). Therefore, nearly all of the environmental contamination is associated with the application of night soil rather than to indiscriminate defecation, and a method of rendering night soil safe could drastically decrease the number of infective stages in the environment.

Biogas as a sanitation-based solution

One sanitary technology that renders night soil safe is the biodigester (BD). BDs are sanitation systems designed for rural use and have been in large-scale use in China since the 1970s. Early designs were inexpensive but of poor quality and, consequently, many BDs fell out of use. The technology has evolved and improved significantly since, and their use has seen a concomitant increase. Within the last decade, the Chinese government has made a sizable commitment to biogas and has expanded biogas programs significantly, primarily as a way of controlling agricultural and human waste and for rural energy production. In 2000, the Ministry of Agriculture implemented the Biohousehold Program and increased its investment in rural biogas development by spending over 6 billion China yuan renminbi (CNY; approximately 6 CNY = 1 USD). This was followed by the announcement of the 2003–2010 National Rural Biogas Construction Plan (revised in 2007). Biogas was an important component of China's "New Socialist Countryside" program announced at the 10th National People's Congress in 2006, and there has been a rapid expansion of rural biogas use during the 11th, 5-yr-plan (2006–2010). In 2007, 60% of China's population (0.9 billion) lived in rural areas (Chen et al., 2010). As of 2007, approximately 139 million rural households were suitable for BD construction but only 26.5 million households are presently using biogas for energy, meaning that only 19% of the biogas potential is being realized in China. Sichuan Province has the most BDs in use (2.94 million) (Chen et al., 2010). The Chinese government has set a national target to increase biogas production from 19 to 44 billion m^3 by 2020 (Anonymous, 2007).

BDs are underground, individual, household-scale anaerobic fermentation chambers that are used to process organic waste. The common "China dome" BD (Fig. 2) is comprised of a large chamber or reactor with an influent port and an effluent chamber. The influent port through which waste enters the reactor is typically connected directly to the toilet and pigpen. Methanogenic bacteria acting on the organic material produce methane and other gases, commonly referred to as "biogas," which collects in the dome of the reactor and is piped directly into the kitchen. Biogas is 50–70% methane and 30–40% CO_2 with lower levels of N_2, water vapor, and hydrogen sulphide. Biogas is odorless and colorless and burns similarly to liquid propane. Digesters operate most efficiently between 30 and 40 C or 50 and 60 C, with an optimum carbon:nitrogen input ratio of 20–30:1 (Dioha et al., 2013). Digestion time ranges from weeks to months, with gas production occurring continuously. Yields of biogas are variable depending on BD design and season. For example, a "6-in-1" BD that utilized human, pig, and chicken waste produced an average of about 4 m^3 of biogas per day in the summer and 1.5–2 m^3 in the winter in northern China (Liu et al., 2001). A more common 8–10 m^3, "3-in-1" household unit (BD, toilet, and pigpen) produces 0.3–0.9 m^3 per day (van Groenendaal and Gehua, 2010). For comparison, 1 m^3 of biogas can provide the equivalent to 6 hr of light from a 60–100 watt bulb or cook 3 meals for a family of 5 (Bates, 2007). Digesters work best with significant amounts of excreta—plants and domestic waste give slow gas yield. Human waste and animal manure from a typical family, together with small amounts of biomass such as weeds, food waste, and crop residue, will meet ~60% of the family's energy needs.

The liquid level in the reactor will decrease as biogas is generated, thereby causing the level in the effluent chamber to rise. Effluent is removed regularly to maintain the headspace and keep gas pressure constant. The effluent is a dark, odorless slurry that can be used as a crop or fish pond fertilizer, an animal feed supplement, or to soak seeds prior to germination. The BD is low maintenance and, if mostly animal waste is used, requires little regular maintenance or cleaning.

BDs are constructed using local materials and labor and can be completed in several days. The cost to build a 3-in-1 unit in Sichuan Province is 4,500 CNY, but the Chinese government will provide a 1,200–1,500 CNY subsidy in the form of construction supplies and new gas appliances (pressure gauge, rice cooker, stove). The toilet and pigpen are usually remodeled and upgraded during BD construction and are connected to the BD.

STH control and other public health benefits of BDs

Diseases associated with poverty and poor sanitation account for approximately 10% of the total global disease burden,

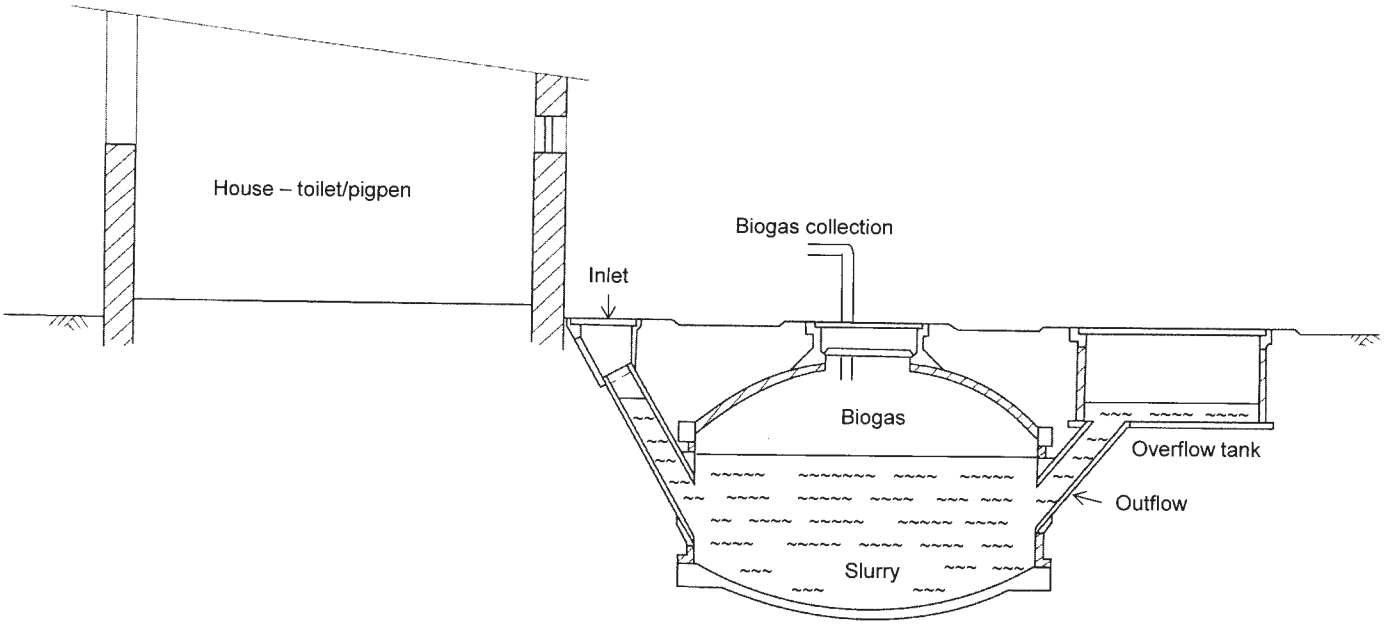

FIGURE 2. Illustration of a typical Chinese fixed dome 3-in-1 biodigester. Waste from the toilet and pigpen is fed into the inlet and undergoes anaerobic fermentation in the chamber, releasing biogas, which is piped into the house for use as fuel. Effluent is removed periodically from the overflow tank and used as a nitrogen-rich fertilizer.

including 4.0% of deaths (Pruss et al., 2002; Prüss-Üstün et al., 2008). Approximately 2.6 billion people lack access to improved sanitation, the majority of which are rural (Mara et al., 2010). Prevention of sanitation and water-related diseases could save approximately $7 billion per year in health system costs and an additional $3.6 billion per year due to deaths prevented (Hutton and Haller, 2004). Each dollar spent on sanitation could generate approximately $10 of economic benefit, primarily from increased productivity gained from improved health (Hutton et al., 2007; Mara et al., 2010).

From a public health perspective, the primary advantage of BDs for human health in China is the destruction of parasites and other infectious agents. BDs achieve this primarily by 2 mechanisms. First, larger organisms such as parasite eggs precipitate during transit of the digestate through the BD. This results in these stages being in the sludge, which remains in the BD for long periods of time. Secondly, anaerobic fermentation generates ammonia that destroys most bacteria, viruses, and parasite eggs. For example, transit through a BD can kill over 99% of the extremely durable *Ascaris* spp. eggs (Liu et al., 2001; Zhang et al., 2001). Using functioning BDs, Remais et al. (Remais et al., 2009) found a 3-log removal of *Ascaris* sp. eggs by precipitation and biochemical inactivation, rendering the effluent essentially parasite free. The residual slurry, containing few if any parasite eggs, is removed at the effluent port and used as a safe, high-N_2 fertilizer. Application of this material as fertilizer instead of fresh night soil will prevent contamination of fields with STH eggs or infective larvae, thereby interrupting transmission and, eventually, leading to STH eradication. The destruction of bacteria and viruses in the excreta also improves overall sanitation and decreases gastrointestinal illness (Fewtrell et al., 2005).

Additional benefits of biogas

In addition to the direct benefits of reducing GI disease and parasite transmission, BDs provide additional benefits that make them even more cost effective and attractive. Almost 3.9 billion tons of animal waste are produced per year in China, most of which is not treated. Also, in 2007 about 600 million tons of biomass plant waste were produced, with more than 40% burned or discarded as worthless (Li, 2006; Jiang et al., 2011). BD technology represents a practical and beneficial way of treating this abundance of organic waste in 2 ways, i.e., the economic value of biogas and effluent and the environmental and health costs of disposing of waste by other means. Waste management is the driving factor behind the Chinese government's biogas expansion effort.

The primary reason a farmer has a digester installed is to produce biogas, which as mentioned, can provide almost 60% of a family's energy needs. The energy savings results in a significantly reduced use of wood fuel, thereby taking pressure off local forests. Large changes in fuel use were reported in a village in Sichuan Province where biogas was introduced, with a 68% decrease in household coal usage and a 74% reduction in wood usage (Remais et al., 2009). Use of BDs will reduce deforestation and habitat destruction by reducing firewood use. For example, in Guangxi Province a family of 5 uses the equivalent of 2,100 kg of firewood as fuel per year (Long, 1992). BDs are an integral part of the efforts by the Nature Conservancy to decrease wood fuel use and the consequent deforestation and habitat degradation in ecologically sensitive areas of Yunnan Province (Anonymous, 2011), where construction of 1 BD saves 0.2 ha of forest and over 2,000 kg of firewood per year (Zhang et al., 2001). Furthermore, it frees people (primarily women) from the chore of collecting firewood, a task that may take up to 1 day per week (Gautam et al., 2009).

Cooking with biogas also eliminates smoke and ash in the kitchen (Remais et al., 2009), thereby decreasing respiratory infections, lung damage, and premature death. Burning of wood, crop residues, and coal is the leading source of indoor air pollution (IAP) globally (Schei et al., 2004; Pant, 2007; Prasad, 2012), causing approximately 420,000 premature deaths per year in rural China alone (Zhang and Smith, 2007). A cleaner and smokeless kitchen is given as a major benefit of biogas by farmers who installed systems (Remais et al., 2009).

Poorly managed or untreated animal manure is a major source of air and water pollution due especially to nutrient leaching, ammonia evaporation, and pathogen contamination. Animal production is responsible for 18% of overall greenhouse gas (GHG) emissions (CO_2 equivalents) and 37% of anthropogenic methane (23× the global warming potential of CO_2), 65% of nitrous oxide, and 64% of ammonia emissions worldwide (Steinfeld et al., 2006). BDs can help mitigate global warming by reducing methane in slurry, as compared to composting organic material aerobically (Srinivasan, 2008), and by producing less CO_2 from burning firewood and fossil fuels (Srinivasan, 2008). In 1 study in a typical agro-village in Shandong Province, an estimated 65.9 tons of standard coal was saved in 2009, thereby reducing CO_2 emissions by 177.9 tons (Zheng et al., 2010). Methane mitigation saves carbon emissions and can be traded as certified carbon emission credits (CER) under the Kyoto Protocol Clean Development Mechanism (CDM, 2011). Under this mechanism, an industrialized country with GHG reduction commitment (Annex B country) can invest in a project that reduces emissions in a developing country rather than in the industrial country. This could offer a mechanism for financing of BD installation over the long term (Chen et al., 2010). In Sichuan province, biogas reduced the global warming commitment of a household by 48–54% compared to households without biogas (Dhingra et al., 2011). Also, a recent report from the United Nations Environment Programme (UNEP) named black carbon from wood fires as a major short-term cause of climate change, and noted that reduction in levels of these particulates would slow the rate of climate change significantly during the first half of the century (UNEP, 2011). Therefore, installation of BDs will help mitigate black carbon-induced climate change as well as decrease respiratory illness.

Another important advantage of BDs is the generation of a high quality, nitrogen-rich fertilizer that is free from parasite infective stages. The fertilizer improves the soil, reduces the need to apply costly commercial fertilizer, and is perceived by the farmer as being superior to fertilizer that has not passed through the BD (Remais et al., 2009). This is supported by research indicating that biogas residue has higher available nitrogen and is superior to compost as a fertilizer (Svensson et al., 2004). Use of BD effluent can increase the net economic yield of a field by 30% over unfermented night soil (Wu and Liu, 1988). BD effluent meets the criteria for "organic" fertilizer, allowing access to the lucrative organic vegetable industry. Also, many farmers raise additional pigs to increase the amount of biogas produced, thereby raising their household incomes when they sell the pigs at market (Remais et al., 2009). Finally, BD installation and maintenance create jobs in the local community for masons, biogas technicians, and extension agents to educate farmers on BD use. These factors, together with biogas energy, represent a significant economic benefit to farmers and their communities (Srinivasan, 2008).

Advantages of biogas for STH control

BDs have several characteristics that make them an extremely attractive strategy for STH control. In surveys of farmers, biogas systems are extremely popular (96% satisfaction) (Remais et al., 2009). Even with government subsidies, installation of a BD will cost on average 23–32% of a household's annual income. This investment is perceived to be worthwhile because the capital cost can be recovered in 2–3 yr with the savings in energy prices, which are valued at approximately 600 CNY per year (Remais et al., 2009). Because the BD provides significant economic return, the farmer bears most of the expense of STH control. This means that the cost of STH control to donors and governments becomes the cost of the subsidy required to incentivize BD installation. This would vary based on local economic conditions and might need to be higher in poorer regions or countries. However, when one considers that a household BD will be used by members of the family, this cost would be spread over several people who would all benefit from fewer infectious stages in the environment as well as from a reduction in diseases associated with poor sanitation. Improved sanitation works for everyone, including those for whom vaccines or anthelmintics are contraindicated. Furthermore, once a BD is installed, its negative effect on STH prevalence and intensity will continue for many years without subsequent annual visits to re-administer treatments. This "once-and-done" aspect will further bend the cost curve down over time, making BD and biogas highly competitive with MDA or vaccines.

More importantly, sanitary systems like BDs may eventually lead to the local elimination of STH infections. In China, where night soil use is responsible for STH transmission, the number of infective stages deposited on the fields will decrease precipitously with the use of BD effluent, thereby interrupting transmission. While it could take many years for BDs to eradicate STH infections in areas of high prevalence, BD installation combined with a single deworming treatment would accelerate the rate of elimination or eradication. On a global scale, sufficient coverage could theoretically lead to eradication of all STH infections. The concepts of elimination or eradication are rarely heard in the context of MDA or vaccines.

Finally, another important advantage of sanitation improvements like BDs over MDA and vaccines is their likely impact on infections with *Strongyloides stercoralis*, the "neglected" NTD. Like hookworms, infective larvae of this intestinal nematode infect humans by skin penetration and, therefore, have a similar epidemiology. Infections with *S. stercoralis* are extremely dangerous, however, due to the nematode's ability to maintain a long, chronic infection through autoinfection and its propensity to undergo a frequently fatal hyperinfection and dissemination in response to immunosuppression or treatment with steroids (Keiser and Nutman, 2004; Buonfrate et al., 2013). *Strongyloides stercoralis* is mostly omitted from discussions of STH control because it is difficult to diagnose and treat within the current MDA paradigm (Requena-Mendez et al., 2013). Estimates based on data from the 1990s of 30–100 million cases are widely agreed to be underestimates (Genta, 1989; Jorgensen et al., 1996; Montes et al., 2010); more likely the number of infections exceeds 370 million (Requena-Mendez et al., 2013). This large underestimate is because the Kato–Katz egg count method used to estimate the prevalence and intensity of other STH infections misses most *S. stercoralis* infections. Another reason *S. stercoralis* is ignored is

that the BZ drugs are ineffective, meaning that current MDA programs to control STH would have little or no impact on *S. stercoralis* infections unless ivermectin is included, a practice which currently occurs only in areas where onchocerciasis or LF are also being targeted (Requena-Mendez et al., 2013). Also, reduction of the worm burden, the goal of current 1-dose MDA programs, is not sufficient with *S. stercoralis* due to its auto-infective cycle. Complete cure is required, which is not feasible in the current MDA program structure.

Advocacy for including *S. stercoralis* infections in control efforts is finally appearing in the NTD literature (Bisoffi et al., 2013; Krolewiecki et al., 2013). Obviously, sanitation-based interventions like biogas would decrease environmental contamination with infective larvae and interrupt *S. stercoralis* transmission, eventually leading to elimination or eradication. Somewhat ironically, proponents of *S. stercoralis* control advocate for inclusion of yet another drug (ivermectin) in current MDA programs or a new vaccine initiative rather than the comprehensive, market-driven, sustainable option of a culturally appropriate sanitary solution like biogas.

Is biogas a global solution?

China has made a massive commitment to renewable energy and expanding biogas production. Along with this expansion will come a decrease in STH transmission, especially as public health officials make the connections and advocate for higher coverage in endemic areas. But can the success of biogas in China be exported to other STH endemic regions of the globe as a control strategy? China is somewhat unique, having been involved in biogas implementation since the 1950s as well as being a leader in the development of BD technology. Furthermore, the culture surrounding night soil use in rural China lends itself to high latrine usage. In areas with open defecation and low latrine coverage, convincing people to use latrines might be more difficult.

Will the energy and other benefits of biogas overcome ingrained cultural behaviors that lead to indiscriminate defecation? To answer this question, a look at the extent of biogas use in other developing countries is instructive. Household biogas technology is spreading to rural areas throughout the world, although none is currently as advanced as China in widespread implementation. The largest gains have occurred in other parts of Asia. India has the second largest number of BDs running, but most are large agriculture-scale plants for the processing of cattle dung (An, 2005; Suryawanshi et al., 2010). However, efforts are underway to extend the technology to the rural poor and to link the BD to toilets to provide for sanitary disposal of human waste and for fertilizer (Anonymous, 2013; PHGDF, 2013). Two Dutch NGOs, the SNV Netherlands Development Organisation (http://www.snvworld.org/), and the international development organization Hivos (www.hivos.org) have actively helped develop and support national biogas programs in multiple countries worldwide (SNV, 2013). The Asia Biogas Program is designed to build a commercially viable biogas sector in Bangladesh, Cambodia, Lao PDR, and Vietnam. By the end of 2012, rural households in Asia outside China had installed 185,000 BDs with this program (SNV, 2012). SNV also helped establish the Biogas Support Program in 1991 to develop the biogas sector in Nepal (Bajgain et al., 2005). There are more than 200,000 biogas plants in operation in Nepal (Sapkota et al., 2012), where the biogas sector employs approximately 11,000 people directly and has been estimated to employ an additional 65,000 indirectly (Gautam et al., 2009). In partnership with Hivos, SNV supports the African Biogas Partnership Program, which aims to build 70,000 BDs in 6 countries (Ethiopia, Kenya, Tanzania, Uganda, Senegal, and Burkina Faso) by 2014, as well programs in Indonesia (8,000 BDs in 4 yr) and Cambodia (65,000 BDs by 2018), Costa Rica, and Honduras (SNV, 2013). The availability of less-expensive tubular polyethylene BDs has allowed expansion of biogas technology into developing countries where the concrete China dome digesters are too expensive for farmers (Lansing et al., 2008). New designs are being explored for use at high altitudes in South America for digestion of llama and guinea pig waste (Ferrer et al., 2011; Garfi, Ferrer-Marti et al., 2011; Garfi, Gelman et al., 2011).

As biogas expands in the developing world, many of the benefits of biogas seen in China are being replicated. Excellent examples of these benefits have been documented in Nepal, which has a fairly well developed biogas sector. Use of biogas is associated with fewer cases of bronchitis and asthma due to the reduction of IAP caused by cooking with wood or dung (Melsom et al., 2001; Pant, 2007). The healthcare costs per year from burning dung bricks, mostly from smoke-induced asthma and eye disease, are 61% higher than the cost of biogas (Pant, 2012). Other human benefits from biogas include improved hygiene, a reduction of up to 3 hr per day spent collecting firewood by women and children, and biogas lighting that allows reading and studying after dark (Gautam et al., 2009). Similar benefits were documented in households using biogas in Kenya where exposure to cooking smoke, time spent collecting wood, money spent to purchase wood, and back pain from carrying wood all decreased significantly (Dohoo, Guernsey et al., 2013; Dohoo, VanLeeuwen et al., 2013). There have also been significant environmental benefits from biogas use in Nepal including reductions in biomass (dung and agricultural residues), kerosene, and fuel wood use (Gautam et al., 2009). For example, biogas use has saved over 14,268 tons of biomass per year, which is equivalent to more than 8,917 ha of forest (Sapkota et al., 2012). Also, the CER of GHGs from each BD is estimated at 2.3 tons annually, and biogas provides Nepal with approximately $400,000 in income from the CDM (Sapkota et al., 2012). Finally, using the effluent from the BD as fertilizer is estimated to save almost $300,000 per year in the cost of imported fertilizer (Gautam et al., 2009).

Obstacles to biogas

Clearly biogas has the potential to revolutionize STH control and provide secondary benefits to both rural health and the environment. Because it is economically desirable, Chinese farmers are willing to invest, knowing they will recoup the cost in decreased energy and health costs within several years. The rate of cost recovery is accelerated by the government subsidy, and the government has made a commitment to expansion of the biogas sector, ensuring that technical support is available. The long tradition of collecting and using night soil as fertilizer, and its associated latrine use, is perfectly compatible with biogas technology. However, the set of conditions that make biogas suited for China may not be present in all developing countries where STHs are endemic. Economic, technical, and cultural

barriers (or a combination) may prevent widespread adoption of biogas in other parts of the world.

Perhaps the largest barrier to the use of BDs to specifically combat STH infections is the lack of connection between the agricultural and energy benefits and the public health advantages of improved sanitation. The driving force behind biogas is typically not disease control but, instead, the processing of animal waste generated in agriculture for energy production. Even China, where night soil is used and household BDs receive human waste, emphasizes these aspects, and the agricultural sector rather than the public health sector is the major advocate for BD use. The positive effects on health that are frequently mentioned are usually those resulting from decreased kitchen smoke and ash as well as improved general hygiene. The public health effects of STH control should be used as an additional driver for biogas expansion into rural areas. Adding the prospect of sustainable STH control to deployment of BDs should increase the appeal to governments and the WHO, as it presents an opportunity to address multiple development goals with a single investment, i.e., sanitation and STH control.

Biogas has been slow to develop in Africa, and the reasons for this will need to be addressed if biogas technology is going to help control STH infections there. Because of the extensive impact these diseases have in Africa, successful STH control and elimination will require widespread adoption of biogas by many countries. Its development has been hindered by the lack of government support for biogas, the absence of coherent energy programs, substandard construction of BDs, and poor maintenance by owners (Arthur et al., 2011). Lack of government support through subsidies and other policies results in high installation costs, which is the largest obstacle to biogas adoption reported by farmers in Africa (Mwakaje, 2008). Part of this problem results from insufficient accounting of indirect benefits, which frequently are not monetized. A cost–benefit analysis needs to include often-neglected indirect effects of BDs in addition to more-easily monetized aspects such as energy savings (Srinivasan, 2008). For example, in some cases BDs make small, or insignificant, savings in household energy use (van Groenendaal and Gehua, 2010). However, when indirect effects are included such as time savings and productivity increases due to improved health from less IAP, GHG mitigation, and improved soil fertility, the benefits become more clear (Srinivasan, 2008). One consideration that has curiously been omitted that would further increase the benefits is the effect of parasites and other infections on overall health.

Technical obstacles to the expansion of biogas in Africa and elsewhere include a shortage of expertise, inadequate training in BD operation and maintenance, and insufficient outreach to farmers regarding fertilizer benefit and usage. Countries without a night soil-based agricultural system, which is essentially all of Africa, might require educational outreach as to the value of BD digestate as a superior fertilizer. Even in China, some theoretical benefits of BD use are not fully realized because of improper use of the effluent for fertilizer. In any case, proper use of the effluent is often not taught to farmers, resulting in increased use of pesticides and chemical fertilizer rather than having the opposite effect. Training and long-term support for farmers installing BDs would alleviate this problem (van Groenendaal and Gehua, 2010). Also, the development of a dynamic market for high quality digestate may be required to realize the full economic benefits of BD fertilizer. This would provide opportunities for local entrepreneurs, perhaps through micro-financing mechanisms. For example, digestate fertilizer could be used by individual farmers to grow organic produce, which commands higher market prices, or alternatively could be sold to larger agribusiness (Srinivasan, 2008).

Finally, cultural factors affecting latrine use and the use of human feces as fertilizer must be addressed, especially in the context of STH control (Mwakaje, 2008; Arthur et al., 2011). In many parts of Africa, biogas is strictly for processing agricultural manure, and BDs are not connected to toilets. In these places, ways to encourage inclusion of human waste will be needed if STH control is to be achieved. This is not always straightforward due to social and cultural conventions (Srinivasan, 2008) and must be approached in a culturally appropriate manner if it is to be successful.

Many of these obstacles are not unique to Africa. Economic benefits, primarily as energy cost savings, are by far the primary motivation for household adoption of biogas everywhere. Indirect benefits of biogas, such as animal and human waste treatment, decreased deforestation, and GHG emissions, are attractive to governments but rarely factor into the farmer's calculus. These benefits are insufficient to entice farmers, who cite the limited availability of information, reluctance to change due to potential risk, and high cost as barriers to adoption of biogas (Srinivasan, 2008). To overcome these concerns, incentives for continued operation may be required in addition to those for building BDs (Srinivasan, 2008). Even in China, those villages that did not receive subsidies had no biogas systems constructed, although farmers said that subsidies played no part in their decision whether to install a BD (Remais et al., 2009). This suggests that the outreach and education that accompanies subsidies is important for adoption of biogas technology by rural farmers. Also, incentive structures and subsidies need to be appropriate for local economic conditions to encourage widespread implementation. Construction techniques, education about proper use, and maintenance need to be improved, perhaps by encouraging small business development to meet the market for these needs. Ultimately, widespread success of BDs and biogas in controlling STH will depend on adapting the technology to be culturally appropriate and economically desirable for each region or country.

What needs to be done?

Biogas technology has tremendous potential to control STH infections in a sustainable way, with the added advantage of simultaneously providing important health, economic, and environmental benefits. In order to reach its potential, several key issues need to be addressed. First, the public health community, particularly the deworming community, needs to establish linkages with the water, sanitation, and hygiene (WASH) community to push this solution forward. Recently, efforts to make connections have begun. In 2012, a group of NTD and WASH experts met to discuss opportunities to collaborate and to identify priorities (Freeman et al., 2013). One obvious way to achieve linkages would be to include sanitation components in MDA programs. Biogas represents an excellent mechanism for this situation because it is an economically driven, bottom-up approach that is not entirely dependent on wealthy benefactors. A

small, locally appropriate incentive can tip the economic balance in favor of biogas, and the return on the investment can take as little as 2–3 yr. There also needs to be an effort to connect BDs to toilets in areas where they are not. In areas that are resistant to latrine use, culturally appropriate anti-open defecation programs can be coupled with BD installation and the economic and health benefits emphasized to overcome resistance.

Second, research into the effects of BD on transmission of STH is urgently needed. Critical questions need to be addressed including whether BD can actually eliminate transmission, and in what timeframe, as well as determining the coverage level needed to effect control. Also, can deworming coupled with BD installation accelerate elimination or compensate for lower coverage levels? Answers to these questions will inform future strategies for STH control and elimination. Finally, the advocacy that is currently devoted to deworming by MDA needs to be turned to more-sustainable control methods such as biogas. Donors and governments must be persuaded to invest in this initially more expensive, but ultimately sustainable, "once-and-done" approach of BD installation and a single treatment for permanent STH control. To adapt an old adage: If you give a man a pill, he is dewormed for a day. If he builds a biodigester, he lives worm-free… and can cook the fish you gave him the first time!

CONCLUSION

By the end of 2011, 2.5 billion people lacked access to improved sanitation. One billion people continue to practice open defecation, 90% of which occurs in rural areas (WHO, 2013). Because of the interrelationship of sanitation and transmission, control efforts that improve overall sanitation within a culturally acceptable framework represent the ideal sustainable prospect for long-term control or even eradication of STH infections. Currently, the goal is to control morbidity from STH infections by using annual MDA in perpetuity. Why not aim for a higher goal, such as eradication of STH, by using culturally appropriate, bottom-up sanitation solutions that can incorporate or run in tandem with MDA programs? Tremendous amounts of money are directed towards deworming that fails to prevent reworming, fails to even approximate established treatment goals, and is ultimately unsustainable. Inexpensive, relatively simple, and highly desirable sanitation interventions like biogas offer long-term, sustainable solutions that will lead towards eradication, thereby helping not only infected children but all persons at risk from STH infection now and in the future.

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