

## Global deworming: moving past albendazole and mebendazole

Since the 2001 adoption of the World Health Assembly (WHA) resolution calling for the global deworming of children affected by soil-transmitted helminth (STH) infections and schistosomiasis,<sup>1</sup> the world's public health leaders have gradually responded. Although we are still behind schedule in terms of the WHA's original 2010 targets, WHO continues to report progress—in 2015, approximately 59% of the world's children requiring treatment received access to deworming medicines for their STH infections,<sup>2</sup> mostly single-dose albendazole or mebendazole (each an anthelmintic drug in the benzimidazole drug class).

But is deworming working? So far, the answer is generally positive, but clearly not all STH infections are created equal, and the global health effect of mass drug administration with single-dose albendazole or mebendazole is more impressive for ascariasis than it is for trichuriasis or hookworm infection. For example, the Global Burden of Disease Study (GBD) 2015,<sup>3</sup> which examined the changes in global prevalence and disease burdens of the major STH infections, showed that the age-adjusted years lived with disability (YLDs) for ascariasis decreased by around 44% between 2005 and 2015, but only decreased by 25% and 23% for trichuriasis and hookworm, respectively. The reductions in prevalence over this period follow a similar trend.

Included among the reasons for the GBD 2015 observations is that hookworm infection is also highly prevalent among adults who do not generally receive deworming medicines, but we also need to consider the inadequacies of the drugs themselves. Although single doses of albendazole or mebendazole are highly effective at removing adult *Ascaris lumbricoides* worms from the intestines, they are not as effective for trichuriasis and hookworm infection.<sup>4</sup> Specifically regarding hookworm infection, there are several reports of outright drug failure using mebendazole, and a systematic review showing that this drug has no effect on hookworm anaemia;<sup>5</sup> failures with single-dose albendazole have also been reported.<sup>6</sup> Such findings might partly account for the variable effects of deworming in randomised clinical trials that examined the host's nutritional status in children with STH infections.<sup>7</sup>

In response, several investigators have called for the development of alternative disease controls

including new anthelmintic drugs or vaccines.<sup>8</sup> In *The Lancet Infectious Diseases*, Wendelin Moser and colleagues<sup>9</sup> report their findings from a randomised trial to treat STH infections in adolescents using alternative anthelmintic drugs, including tribendimidine—a broad-spectrum anthelmintic drug first developed during the 1980s in China, which was subsequently shown to function as a nicotinic acetylcholine receptor agonist similar to two older-generation anthelmintic drugs used in human beings, levamisole and pyrantel.<sup>10</sup>

Working in Tanzania and Cote d'Ivoire, Moser and colleagues used parasite egg-reduction rates (ERRs) against hookworm infection (measured by the Kato-Katz method) as a primary outcome, assessing coadministered tribendimidine treatments for non-inferiority against albendazole plus oxantel pamoate (using a margin of 3 percentage points), with safety and cure rates as secondary outcomes, in addition to ERRs for *A lumbricoides* and *Trichuris trichiura* infections.<sup>9</sup> They showed that tribendimidine plus ivermectin was non-inferior to albendazole plus oxantel pamoate for the primary outcome (ERR 99.5% [95% CI 99.2–99.7] vs 96.0% [93.9–97.4]; difference: 3.52 percentage points [95% CI 2.05–5.65]). Additionally, in a post-hoc analysis, the investigators noted that tribendimidine plus ivermectin was superior to tribendimidine monotherapy for both hookworm infection and trichuriasis, whereas tribendimidine combined with oxantel pamoate was superior to tribendimidine monotherapy for trichuriasis but not for hookworm.<sup>9</sup> All the combinations worked well for ascariasis.<sup>9</sup>

Overall, tribendimidine showed similar efficacy to albendazole, combinations of tribendimidine plus ivermectin had the highest efficacy against hookworm, and tribendimidine plus oxantel pamoate might be the best treatment for trichuriasis.<sup>9</sup> An overriding point of the study is that tribendimidine could be an alternative to albendazole, especially if anthelmintic drug resistance develops as has been shown for drugs of the benzimidazole class against veterinary parasites.<sup>11</sup> However, to cure all three STH infections with a single dose, new drug combinations such as those outlined earlier will be required.<sup>9</sup>

As global deworming continues to expand in its second decade, either because of concerns about benzimidazole drug resistance, or because of general



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disenchantment about the prospects of single-dose albendazole or mebendazole eliminating hookworm or trichuriasis, new approaches need to be envisioned. Potentially, tribendimidine combinations with either ivermectin or oxantel pamoate might offer some alternatives, but even then anthelmintic drugs of the acetylcholinesterase inhibitors are well known to be highly susceptible to emerging drug resistance.<sup>11,12</sup> Therefore, the search for optimum approaches and new technologies for global deworming will need to continue.

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