GiveWell

INTERVENTION REPORT

Combination Deworming (Mass Drug Administration Targeting Both Schistosomiasis and Soil-Transmitted Helminths)

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In a nutshell

This page discusses the general case for mass deworming. We focus our discussion on work similar to that of deworming programs implemented by several of our **top charities**.

Mass deworming involves treating large numbers of people with parasite-killing drugs: praziquantel kills the parasites that cause schistosomiasis, while albendazole kills soil-transmitted helminths. Treatment is cheaper than diagnosis and usually takes place in areas where worms are fairly common. Also, side effects of the drugs are believed to be minor; thus, everyone in a given population (sometimes schoolchildren; sometimes the community at large) is treated, without being individually tested for the presence of infections.

Mass deworming is generally very inexpensive on a per-person-treated basis (in the range of $0.50). The benefits are potentially major, but also debatable: parasitic infections rarely cause mortality or other acute effects, and the evidence on their impact on quality of life is thin. In brief:

- There is strong evidence that administration of the drugs reduces worm loads, but weaker evidence on the causal relationship between reducing worm loads and improved life outcomes.
- Evidence for the impact of deworming on short-term general health is thin. We would guess that deworming has small impacts on weight, but the evidence for its impact on other health outcomes is weak.
- A series of follow-ups to one experiment (**Miguel and Kremer 2004**) finds that reducing worm infection loads during childhood can have a significant later impact on income. We find these studies to constitute evidence that is suggestive, though not conclusive or necessarily representative (the intensity of worm infections in this study was substantially heavier than the intensity of worm infections in most contexts where deworming is carried out today). We provide a deeper overview of the evidence for long-term effects of deworming below and at two blog posts: **here** and **here**.
- Attempts to estimate the cost-effectiveness of deworming within the **disability-adjusted life-year (DALY) framework** have been problematic. In 2011, GiveWell found the figures published by the World Health Organization to be **off by ~100x due to errors** and **flawed in other ways even once corrected**.

- Cost-effectiveness calculations are extremely sensitive to many assumptions, but our best guess is that deworming is comparably cost-effective to our **priority programs** (**more**).

Previous versions of this page:

- **2015 deworming report**
- **2014 deworming report**
- **2013 deworming report**
- **2012 deworming report**
- **2011 deworming report**
- **2009 deworming report**

What are the infections targeted by mass deworming, i.e., soil-transmitted helminthiasis (STH) and schistosomiasis?

"Schistosomiasis" and "soil-transmitted helminthiasis (STH)" both describe chronic parasitic infections. We discuss each below.

Schistosomiasis

Schistosomiasis involves infection with parasites released by snails and transmitted through the skin when it is exposed to infested water.[1] The most common species of schistosoma infections in humans are *S. mansoni, S. haematobium,* and *S. japonicum*.[2]

While *S. japonicum* is present primarily in Asia and the Pacific, *S. mansoni* and *S. haematobium* are found in much of the tropics, including Sub-Saharan Africa.[3] There is disagreement about how common schistosomiasis infections are; estimates range from 200 million to more than 600 million people infected.[4] The **Schistosomiasis Control Initiative** treats schistosomiasis and STH while the **Deworm the World Initiative** mainly treats STH. Since the **Schistosomiasis Control Initiative** works mainly in Africa, we focus here on the morbidity caused by those species present in Africa, *S. mansoni* and *S. haematobium*. *S. japonicum* is believed by some scholars to be more dangerous than the other strains that cause schistosomiasis.[5]

The pathology of schistosomiasis varies by species and infection intensity. *S. mansoni* tends to infect the intestines, liver, and spleen,[6] while *S. haematobium* typically infects blood vessels near the bladder.[7]

The burden of infections is typically highest in children and young adults and gradually declines as people age (even without treatment).[8]

In general, the morbidity caused by schistosomiasis arises from the eggs that the parasite lays while it inhabits the human host.[9] Symptoms can include:

- Hematuria (blood in the urine) or dysuria (painful urination);[10] anemia and other nutritional deficiencies.[11] Because these symptoms can have many causes, particularly in very poor populations (where schistosomiasis tends to be most prevalent), it is difficult to pinpoint the extent to which schistosomiasis contributes to them; the best information we have on this question comes from studies of deworming, which we discuss **below**.
- Urinary tract infections and other bladder problems at late stages of the disease, potentially leading to bladder cancer and kidney failure;[12] bloody diarrhea, bloody stools, abdominal pain, and liver failure;[13] death.[14] As discussed **below**, death due to schistosomiasis is quite rare; we have no good quantification of the contribution of schistosomiasis to non-fatal problems along these lines.
- Developmental effects. There is some evidence that schistosomiasis and/or STH impair development and can lower quality of life over the long term. We discuss this further **below**.

Some, but not all, symptoms of schistosomiasis are reversible with treatment.[15]

Soil-transmitted helminthiasis (STH)

Soil-transmitted helminthiasis (STH) includes trichuriasis (or whipworm infection), hookworm infection, and ascariasis (or roundworm infection). Each is estimated to affect the following number of people worldwide:[16]

- Trichuriasis: 604-795 million people
- Hookworm: 576-740 million people
- Ascariasis: 807-1,121 million people

The ascariasis and trichuriasis worms feed on the contents of the intestines, while hookworms feed on host blood in the small intestine, moving frequently and leaving small bleeding sores behind.[17]

People can be, and often are, infected by multiple worms (and multiple species of worms) at once.[18]

The prevailing understanding of soil-transmitted helminths is that many cases are asymptomatic and that morbidity depends on the intensity of infection.[19] Symptoms can include:

- Anemia and other nutritional deficiencies.[20] Because these symptoms can have many causes, particularly in very poor populations (where STHs tend to be most prevalent), it is difficult to pinpoint the extent to which STHs contribute to them; the best information we have on this question comes from studies of deworming, which we discuss **below**.
- Intestinal obstruction,[21] inflammation of the colon,[22] and death.[23] As discussed **below**, the non-fatal effects are generally rare and brief in duration.
- Developmental effects. There is some evidence that schistosomiasis and/or STH impair development and can lower quality of life over the long term. We discuss this further **below**.

How does mass deworming work?

Mass deworming is intended for areas with fairly high prevalence of the infections discussed here; people are treated without being individually tested.

- For STH, the World Health Organization recommends treatment with albendazole or mebendazole, with frequency of administration varying with prevalence of infection.[24]
- For schistosomiasis, the World Health Organization recommends treating school-aged children and other at-risk populations with praziquantel, with frequency of administration varying with prevalence of infection.[25]

Distributions target preschool-age children, school-age children, or the population at large.[26] The **Disease Control Priorities Report** states that schools provide a strong infrastructure and that teachers can be trained to deliver drugs safely.[27]

A fuller picture of the process can be gained from our **notes on our visit to a stakeholders meeting for a national deworming program and a demonstration deworming, as guests of the Schistosomiasis Control Initiative**.

Does mass deworming have a strong track record?

Strong evidence suggests that mass deworming reduces the prevalence of the infections discussed here.

- There are two **Cochrane** reviews of randomized control trials of mass drug treatments for schistosomiasis (primarily using praziquantel, though occasionally metrifonate or oxamniquine). They both conclude that praziquantel is effective in treating schistosomiasis.[28]
- A 2000 meta-analysis found that mass treatment with albendazole was effective in decreasing the prevalence of all three soil-transmitted helminths, though more so for ascariasis than hookworm or trichuriasis.[29]

What are the benefits of mass deworming?

Below, we discuss three major potential consequences of schistosomiasis/STH infections:

- **Impacts on general health**: Evidence for the impact of deworming on short-term general health is thin. We would guess that deworming has small impacts on weight, but the evidence for its impact on other health outcomes is weak.
- **Severe symptoms** such as intestinal obstruction and major organ damage. These occur in only a very small proportion of those infected, so they do not play a significant role in our analysis of the benefits of deworming.
- **Developmental effects**. There is some evidence that schistosomiasis and/or STH impair development and can lower quality of life over the long term. These potential effects are the primary benefits that we estimate from deworming interventions.

We address each of these separately below, and then discuss other possible effects about which less is known.

Impacts on general health

In this section, we first discuss the effect of deworming on weight and haemoglobin levels (low haemoglobin indicates anemia).[30] These are the two health outcomes for which we have done the most analysis. We then discuss the evidence we have seen on other immediate impacts of deworming; this evidence is very limited.

Weight

Our best guess is that deworming likely had small impacts on weight in the contexts in which it was previously studied.

Three separate, recent systematic reviews have assessed the effect of deworming on weight. GiveWell Senior Advisor David Roodman summarizes the estimates from these reviews in **this blog post** and concludes, "The three reviews are best seen as converging to a central impact estimate of about 0.1 kg of weight gain." See **the blog post** for more detail.

Haemoglobin levels

The estimated effects of deworming on haemoglobin levels can vary significantly by context and by one's approach to selecting and combining studies. Our best guess is that any effects of deworming on haemoglobin levels are likely to be small.

We previously conducted **a detailed review** of literature reviews and studies discussing the impact of deworming on changes in haemoglobin levels and concluded that treating children pre-screened for schistosomiasis and combination (STH and schistosomiasis) deworming appeared to increase haemoglobin levels, while it was unclear whether STH-only deworming increased haemoglobin levels.[31]

However, two recent updates to Cochrane meta-analyses appear to be more negative than previous versions of the meta-analyses that we relied on in previous versions of our deworming intervention report.[32] **Taylor-Robinson et al. 2015** does not find evidence that STH deworming affects haemoglobin levels (either in mass deworming programs or in a sub-analysis of studies that only treated infected children), and **Kramer et al. 2014** appears to find that multiple doses of the drug metrifonate may affect haemoglobin levels but does not find effects

on haemoglobin from providing a single dose of praziquantel (the deworming drug delivered by groups like the Schistosomiasis Control Initiative); we have not seen a recent meta-analysis that combines studies of metrifonate and praziquantel to determine the effect of any schistosomiasis treatment on haemoglobin.[33]

We have not yet reviewed these new meta-analyses in detail to determine how to reconcile them with the findings of our previous review. We have not prioritized this investigation since our best guess is that any effects on haemoglobin levels in modern contexts are likely to be small; effects on haemoglobin do not play a major role in **our cost-effectiveness estimates**.

Other general health effects

Our best guess is that, in most cases, deworming does not have a large impact on other general health indicators.

Two recent systematic reviews of STH deworming, conducted by the Cochrane Collaboration and Campbell Collaboration (**Taylor-Robinson et al. 2015** and **Welch et al. 2017**), find that deworming did not have an impact on outcomes such as cognition, height, and school performance.[34]

Welch et al. 2017 concludes that mass deworming for schistosomiasis alone "might slightly increase weight (0.41 kg, 95% CrI −0.20 to 0.91) and has little to no effect on height (low certainty evidence) and cognition (moderate certainty evidence)."[35]

We have not reviewed the above meta-analyses in detail. We are aware of an argument that effects of deworming on health indicators may be too small for mass deworming studies to pick up. We have not yet conducted formal analysis on this topic and have not determined the minimum effect sizes that were detectable in these meta-analyses.

Prevention of potentially severe effects

In addition to subtle general health effects, deworming may avert more severe symptoms. Schistosomiasis can cause organ damage, particularly to the bladder, liver and kidneys, sometimes resulting in death, though these deaths appear highly infrequent and we have little

information about the extent of non-fatal organ damage. Severe symptoms of STH appear infrequent and short in duration.

Schistosomiasis

We have only identified one review[36] (referred to here as "Van der Werf et al.") that systematically attempts to attribute severe symptoms (organ damage/malfunction, death) to schistosomiasis. This review discusses symptoms such as the presence of abnormal amounts of blood in the urine, self-reported painful urination, enlarged liver/spleen, and various signs of kidney stress or malfunction.[37] However, this review is problematic for several reasons:

- We find its methodology for attributing mortality/morbidity to schistosomiasis to be highly problematic.[38]
- It estimates 280,000 annual deaths due to schistosomiasis;[39] by contrast, the official burden of disease publication released by the World Health Organization in 2008 estimates 41,000 deaths.[40] Because the latter cites Van der Werf et al., (2001)[41] we take this as further evidence that the methodology used in Van der Werf et al. is problematic.
- Nearly all of the schistosomiasis consequences discussed in Van der Werf et al. (a) can sometimes be attributable to factors other than schistosomiasis; (b) range in severity and do not necessarily have any detectable impact on quality of life.[42]

Outside of this review, the only quantified information we have found on severe consequences of schistosomiasis involves deaths. It appears to us that even attributing deaths to schistosomiasis is very difficult, and estimates vary widely.[43] Nonetheless, we regard the World Health Organization's 2004 estimate (published in 2008) of 41,000 deaths as the most credible.[44] By comparison, the same source estimates that malaria results in roughly 890,000 deaths a year, more than twenty times as many, the vast majority of which are in children under 5.[45]

We can also get a sense of how bad the *non-death* burden of schistosomiasis is estimated to be, using the World Health Organization's **disability-adjusted life-year (DALY) estimates**. For each age group, we tabulated the ratio of DALYs (a measure of *all* manifestations of disease burden) to YLLs (comparable to DALYs but only addressing mortality).[46] These figures estimate that death accounts for about 80-90% of the burden of disease in people age 15-29; 90%-94% in people age 30-44; 95%+ in people age 45+; and only 10-20% in people under 14. This picture is consistent with the idea that older people are more likely to die due to schistosomiasis, while

younger people are more likely to suffer other consequences such as **subtle impacts on general health** and **developmental effects**.

STH

The serious effects of soil-transmitted helminth infections vary by species.[47] Because these severe symptoms are quite rare, we have found characterizing their frequency and severity to be difficult. The most thorough and up-to-date overview that we are aware of is the chapter on intestinal nematode infections (another name for soil-transmitted helminths) in the World Health Organization's *The Global Epidemiology of Infectious Disease* publication. That chapter is the published version of the working paper that was used to generate the **Disease Control Priorities report**'s **cost-effectiveness estimate for soil-transmitted helminth treatment**.

For ascariasis, the most serious complication is short-term intestinal obstruction, sometimes resulting in death.[48] We estimate that, each year, intestinal obstruction (which may require hospitalization and surgery and has an estimated duration of ~4 weeks) would occur in .026% of the school-age population of Sub-Saharan Africa (1 in ~3800 children per year) without treatment,[49] resulting in about 3 deaths per million children per year of the school-age population.[50]

For trichuriasis, heavy infections can result in a "dysenteric form" involving a bleeding/inflamed colon, discomfort and bloody stools, with a duration of 12 months or more[51]; this is estimated to occur about once a year per ~700 school-aged children in Sub-Saharan Africa each year.[52] It is unclear whether trichuriasis causes mortality, but if it does, this is quite rare.[53]

Hookworm infection's most serious symptom is believed to be anemia.[54] We discuss this symptom **above** and conclude that there is not strong evidence for an impact of deworming treatment on anemia; any such impact is likely to be small.

It appears that the WHO has recently revised its estimates for STH deaths substantially downward. The World Health Organization's Global Burden of Disease report for 2001 (published in 2006) listed 1,000 deaths per year in sub-Saharan Africa for each of ascariasis and trichuriasis and 2,000 for hookworm, for a total of 4,000;[55] but the Global Burden of Disease report for 2004 (published in 2008) lists a total of 412 deaths in sub-Saharan Africa (for the 3 infections combined).[56]

In **Awasthi et al. 2013**, discussed in greater detail **above**, deworming of ascaris and hookworm resulted in a 5% reduction in risk of death between ages 1-6 from 2.65% to 2.52%, though the result was not statistically significant.[57]

Developmental impacts

In our view, the most compelling case for deworming as a cost-effective intervention does not come directly from its **subtle impacts on short-term health** (which appear relatively minor and uncertain) nor from its **potential reduction in severe symptoms of disease effects** (which we believe to be rare), but from **the possibility that deworming children has a subtle, lasting impact on their development and thus on their ability to be productive and successful throughout life**.

Empirical evidence on this matter is very limited, resting primarily on one series of experiments stemming from **Miguel and Kremer 2004**.

Short-term effects from Miguel and Kremer 2004

Miguel and Kremer 2004 involved combination deworming, without prescreening, for some children and STH-only treatment for others (depending on the prevalence of schistosomiasis in the area).[58] The program was not technically randomized but used a method we consider similar to randomization to determine who was treated.[59] It found a ~25% reduction in school absenteeism, though no effect on test scores.[60] It also found statistically significant impacts on self-reported sickness (both for "last week" and "often"), marginally significant results on height, and non-significant results on weight.[61]

Follow-ups to Miguel and Kremer 2004

The below studies are follow-ups to **Miguel and Kremer 2004**. These studies analyzed data on children and young adults who had been involved in the deworming program in grade school, typically comparing children who started receiving deworming treatment earlier to those who started receiving it later.

- **10-year follow-up**: **Baird et al. 2016** compared the first two groups of schools to receive deworming (as treatment group) to the final group (as control); the treatment group was assigned 2.41 extra years of deworming on average.[62] The study's headline effect is that as adults, those in the treatment group worked and earned substantially more,[63] with increased earnings driven largely by a shift into the manufacturing sector.[64] The study also found a positive impact on meals consumed, though not on overall consumption,[65] and gains on self-reported health, though not on height or weight-for-height (and the treatment group had higher health expenditures).[66] While the participants were still in school, the treatment group experienced small, non-statistically significant positive effects on school performance (though not on general intelligence).[67]
- **5-year follow-up**: **Baird 2007 (unpublished dissertation)** analyzes a similar, early dataset from the same program, though it uses a different definition of "treatment group" than the later paper: while **Baird et al. 2016** uses the first two groups of schools to receive treatment as its treatment group and the last as its control, **Baird 2007 (unpublished dissertation)** simply looks at the number of years of deworming assigned to each child.[68] It finds contrasting, though also encouraging, results: some statistically significant impacts on height and weight years after the intervention,[69] little to no impacts on education and labor market outcomes,[70] and small but mostly insignificant negative impacts on cognitive performance.[71]
- **15-year follow-up**: We have seen preliminary, confidential results from a 15-year follow-up to **Miguel and Kremer 2004**. We are not yet able to discuss the results in detail, but they are broadly consistent with the findings from the 10-year follow-up analyzed in **Baird et al. 2016**.

We see the above studies as the most important evidence for the potential long-term effects of deworming. However, there are also two supplementary data points from long-term follow-ups to **Miguel and Kremer 2004** that we believe provide some support for long-term effects, though they carry less weight in our conclusions:

- **10-year follow-up to a younger cohort who may have benefited from spillovers**: **Ozier 2015** assesses the impact of **Miguel and Kremer 2004**'s intervention on infants who were not directly treated but lived in the same communities as treated children. These infants may have benefited from spillover effects (i.e. if fewer children in a community had infections because they were dewormed, then younger untreated children may have been less likely to acquire infections). **Ozier 2015** concludes, "Ten years after the intervention, I find

large cognitive effects—comparable to between 0.5 and 0.8 years of schooling—for children who were less than one year old when their communities received mass deworming treatment."[72] We have not yet carefully reviewed and replicated this study; we may conduct further analysis on this study in the future.

- **Follow-ups to cost-sharing experiment**: **Kremer and Miguel 2007** was a randomized controlled trial conducted in the same sample of children studied in **Miguel and Kremer 2004**. It randomly assigned a group of schools to a treatment condition in which parents were required to pay a fee (which it refers to as "cost-sharing") in order for their child to receive deworming treatment.[73] It found that making treatment conditional on payment reduced take-up by about 80%.[74] **Baird et al. 2016** assesses the long-term effects of randomly being assigned to the cost-sharing group and finds that this group (which received less deworming) experienced negative effects on outcomes such as hours worked, meals eaten, and log wage earnings; these results are only sometimes statistically significant, with significance often depending on details of regression specifications.[75] Though the estimates are imprecise, it appears that the effect size on earnings from receiving less deworming due to cost-sharing is roughly consistent with what would be expected given the estimate of deworming treatment on earnings in the core deworming treatment group from **Baird et al. 2016**.[76]

We have done a variety of analyses to assess the robustness of the core findings from **Baird et al. 2016**, including reanalyzing the data and code underlying the study, and the results have held up to our scrutiny. For more information, see:

- A reanalysis that we conducted in 2012 in order to explore several reservations we had about the study: see our **2012 blog post** and **full writeup**. Our examination resulted in an overall higher level of confidence in the studies than we had had previously, though many concerns remain.
- We wrote a **July 2015 blog post** about our views on two re-analyses of **Miguel and Kremer 2004** and an updated Cochrane review on deworming published in 2015. These studies did not substantively change our conclusions.
- GiveWell Senior Advisor David Roodman assessed the overall case for deworming and the ongoing debate over its effects in 2016; blog posts summarizing this work can be found **here** and **here**.

However, we continue to believe that there are reasons to be cautious in interpreting **Miguel and Kremer 2004** and follow-up studies:

- The conditions at the time of treatment are unlikely to be representative of other contexts: there was extraordinary flooding in the study area due to the El Niño climate pattern, which led to abnormally high prevalence of heavier worm infections.[77]
- In general, we hesitate to place too much weight on a finding from a single study (or a small number of studies) because of the potential for **publication bias** as well as possible alternative explanations for the findings. For example, efforts to encourage students to attend school in order to receive treatment might have bled over to later days, increasing attendance in treatment schools over the following years. The particular piece of data that led us to examine this possibility is that within schools, there is no statistically significant difference in attendance rates for treated and untreated students (the effects only appear across schools). (The authors assume that this phenomenon occurred due to the presence of within-school **externalities**.)
- For further discussion of potential limitations of these studies, see **Jullien, Sinclair, and Garner 2016** and commentary responding to the paper, including David Roodman's response (**Roodman 2017, comment on Jullien, Sinclair, and Garner 2016**).

Other studies of long-term effects

In previous versions of this report, we discussed two other studies that analyzed the long-term effects of deworming campaigns and found positive impacts on outcomes such as cognitive test scores and income: **Croke 2014** and **Bleakley 2007**. However, after further investigation and updates based on new data, we no longer believe that these studies provide substantial support for the theory that deworming has long-term impacts. The below updates have weakened the support for long-term impacts:

- **Croke 2014** followed up on a randomized controlled trial (RCT) of a deworming program in Uganda and found higher scores on tests of literacy and numeracy in children living in treatment areas compared to the control 7 to 8 years later.[78] Since publication of **Croke 2014**, four additional years of relevant test score data have become available. After adding this new data into the analysis, Croke finds that the effects of deworming on test scores remain positive but are statistically indistinguishable from zero. This updated analysis is not yet published, but we have corresponded with author Kevin Croke, and he aims to publish this update in the next year.

- **Bleakley 2007** analyzes the Rockefeller Sanitary Commission's campaign to eradicate hookworm in the American South in the early 20th century and concludes that there is suggestive evidence that this campaign had short-term effects on school enrollment, attendance, and literacy, and long-term effects on income.[79] However, GiveWell Senior Advisor David Roodman has conducted a detailed replication and reanalysis of these findings and has concluded that they do not provide robust suggestive evidence for the hypothesis that deworming had substantial life impacts. For more information, see **this blog post** and its accompanying report, **Roodman 2017, replication and reanalysis of Bleakley 2007**.

Bottom line on developmental effects

We find it highly plausible that deworming has subtle but significant developmental effects that improve quality of later life. The studies on this topic have substantial limitations, and we do not consider them conclusive evidence for the presence (much less for the size) of these effects, even in conditions similar to those in the trials. We do consider them suggestive evidence, enough to take the possibility of developmental effects seriously.

We further discuss how strong we find the case for developmental effects of deworming to be, in comparison with the case for long-term effects of other interventions, in a **2012 blog post**.

Externalities for the untreated

It is possible that deworming benefits people who do not receive treatment by reducing overall prevalence of worm infections in a community. The only evidence we have seen for this idea comes from the same Kenya program **discussed above**. Miguel and Kremer 2004 found significant impacts on children in nearby but untreated schools.[80] In addition, **Ozier 2011** (an earlier version of **Ozier 2015**) reviewed later data on younger children, and concluded:

Community deworming before a child's first birthday brings about a 0.2-standard-deviation improvement in performance on Raven's Matrices, a decade after the intervention. Estimated effects on vocabulary measures are similar in magnitude, but not always as significant; effects on memory are not statistically distinguishable from zero. A summary measure, the first principal component of all six cognitive measurements, also shows a roughly 0.2-standard-

deviation effect. These effects are equivalent to between 0.5 and 0.8 additional grades in school ... The effect of community deworming spillovers on height, height-for-age, and stunting all appear statistically indistinguishable from zero.[81]

For reasons discussed **above**, we believe these studies are likely to overstate the impact of deworming, and that this overstatement is particularly likely to be an issue for externalities due to the unusual flooding and elevated level of infections. In addition, we note that the unusual design of Miguel and Kremer 2004 (in which nearby schools were assigned to be dewormed earlier or later in an essentially arbitrary way) is unlikely to be representative of large-scale school-based deworming campaigns such as those of the **Schistosomiasis Control Initiative** or **the Deworm the World Initiative**.

That said, we think it is worth noting the possibility of externalities, as this could both (a) increase the cost-effectiveness of deworming beyond what we estimate **below**; (b) imply that some of the research on deworming reviewed **above** may understate the impact of deworming because "control" groups may have actually been positive affected by deworming.

Possible negative/offsetting impact

- **Impact on the routine health system**. **Cavalli et al 2010**, a study of a mass deworming campaign in two rural districts in Mali, states: "At point of delivery, campaign-related workload severely interfered with routine care delivery which was cut down or totally interrupted during the campaign, as nurses were absent from their health centre for campaign-related activities."[82]
- **Side effects of drugs**. Albendazole and praziquantel may both have side effects, including headache, abdominal pain, upset stomach, nausea, vomiting, and fever.[83] These effects seem better-understood, and potentially painful but temporary, for praziquantel. There are some more serious claims for albendazole (adverse effects on growth; "reports of elevated liver enzymes, headaches, loss of hair, low levels of white blood cells (neutropenia), fever, and itching if taken at higher doses and/or for a long period of time");[84] we do not have evidence on these, but note that albendazole treatment (as discussed above) seems to generally have effects that are positive or else not statistically significant.
- **Possible development of drug resistance**. The widespread use of deworming drugs may cause resistance to emerge, as has already occurred in STH of livestock.[85] As far as we know,

there is no strong evidence of resistance among human STHs, but we have not deeply investigated this question.[86]

- **Possible transmission of disease via deworming pills.** If those administering or taking deworming pills have dirty hands, they may transmit disease while administering/taking the pill.
- **Choking on deworming pills. Taylor-Robinson et al. 2012**, the Cochrane review on STH-only deworming, notes the possibility that children might choke on deworming pills and cites the WHO's concerns about the issue.[87] An article in "The Times of India" reported in 2012 that a child died in Hyderabad by choking on a deworming tablet.[88]
- **The effect of deworming on malaria. Nacher 2011** reviews observational studies and RCTs on the interactions between worm infections and malaria.[89] Based on **Nacher 2011** and our own search for studies, we know of 5 RCTs examining the effect of deworming on malaria (**Brutus et al 2006**, **Brutus et al 2007**, **Kirwan et al 2010**, **Wiria et al 2013** and **Kinung'hi et al 2015**).[90] We summarize the RCTs below and tentatively conclude that anti-helminthic treatment may increase malaria parasitemia (i.e., the presence of malaria parasites in the blood) and/or the density of malaria parasites in the blood in school-aged children, but scant evidence supports an increase in incidence of symptomatic malaria cases or greater severity of malaria cases due to deworming. We note, however, that the relationship between deworming and malaria seems complex and poorly understood.[91]
  - **Brutus et al 2006** found that levamisole, an anti-helminthic, increased the density of P. falciparum (malaria parasites) in blood samples in school-aged children compared to a control group in a rural area of Madagascar.[92] The study found no apparent effect in children under 5 years old.[93] The study also reported that 2.5% of the control group and 3.3% of the treatment group received chloroquine (treatment for malaria) after presenting with fever and parasitemia over the course of the study.[94] The study population had an infection rate of around 27% for Ascaris lumbricoides, around 9% for Schistosoma mansoni, and around 9% for Necator americanus.[95]
  - **Brutus et al 2007** appears to have found similar results as **Brutus et al 2006** with a similar study design also in a rural area of Madagascar though one at higher altitudes and with different malaria and worm transmission patterns.[96] The study population had an infection rate of around 59% for Ascaris lumbricoides, around 44% for Schistosoma mansoni and close to 0% for Necator americanus.[97]
  - The treatment group in **Kirwan et al 2010** had a statistically significantly higher Plasmodium (malaria parasite) prevalence and average Plasmodium parasite density than

the control group at baseline.[98] However, the study concluded that albendazole slowed an increase in the odds of having a Plasmodium infection in the treatment group over the course of the study compared to the control group (both groups consisted of children between 12 and 59 months old).[99] The study population had an infection rate of around 46% of Ascaris lumbricoides, around 3% of Trichuris trichiura, around 4% of hookworm and around 1% of Schistosoma haematobium.[100]

- **Wiria et al 2013** concluded that albendazole led to a transient increase in malaria parasitemia in school-aged children compared to a control group.[101] The study did not find a statistically significant difference in the incidence of fever and additional malaria-like symptoms between the albendazole group and the placebo group.[102] The study population had an infection rate of around 76% for hookworm, around 34% for A. lumbricoides, around 2% for S. stercoralis, and around 28% for T. trichiura.[103]
- **Kinung'hi et al 2015** did not find a significant difference in malaria prevalence, parasite density or frequency of malaria attacks between a group of pre-school aged and school-aged children receiving praziquantel and albendazole four times a year and a group receiving praziquantel and albendazole once a year.[104] The study population had an infection rate of around 60% for S. mansoni, around 23% for S. haematobium, and around 19% for hookworm.[105]

Different versions of the intervention

How often do people need to be treated?

The World Health Organization recommends annual treatment for schistosomiasis and twice-annual treatment for soil-transmitted helminths for preschool- and school-aged children in areas with prevalence above 50%.[106] In areas with lower prevalence, the World Health Organization recommends less frequent deworming.[107] We have not been able to fully understand the rationale for the World Health Organization's recommendations. The underlying principle is that reinfection rates are higher in areas with greater prevalence, so more frequent deworming will be necessary to avoid morbidity in those areas, but we have not found evidence that shows the superiority of annual treatment (as compared with, e.g., semi-annual or bi-annual treatment).

The World Health Organization's recommendations about which groups of people to treat also vary with prevalence; in low-prevalence areas, treatment is restricted to preschool- and school-aged children and certain categories of adults.[108] We do not know how the cost-effectiveness of treating adults in high-prevalence areas compares with the cost-effectiveness of treating children.

The main reason for focusing deworming treatment on children is that, with the exception of hookworm, the prevalence of the helminths and schistosomes is highest in childhood.[109] Although deworming in childhood does not prevent adults from being reinfected with new worms, the theory underlying mass treatment is that it does prevent the developmental effects of having worms in childhood and the serious organ damage that can result from long-term high-intensity infections.[110]

We believe it is important that deworming programs are sustained over time, as re-infection is rapid and a one-time treatment may have little long-term effect.[111] We have not yet deeply investigated whether it may be more cost-effective to aim for elimination of worms (i.e., treating everyone in a community to eliminate transmission of worm infections) than control of worms (i.e., reducing infections through school-based deworming programs as typically conducted by deworming charities). We have had one conversation with DeWorm3, an initiative that plans to test the feasibility of elimination of worms in the field (**GiveWell's non-verbatim summary**

of a conversation with DeWorm3, February 24, 2016) and we are aware of some relevant studies such as **Lo et al. 2015**.

How cost-effective is mass deworming?

See the most recent version of our deworming cost-effectiveness analysis on **this page**.

We have attempted to quantify *longer-term developmental impacts* by working off of the effects found in the **Kenya studies discussed above**, and making adjustments for what we perceive as unrepresentativeness or other questions around these studies.

We have attempted to quantify *short-term health impacts* using information from the **Disease Control Priorities Report**. Doing so has raised substantial challenges. We have found **significant errors in this report's analysis** that stood uncorrected in the several years between the report's publication and our 2011 investigation, and estimates of the frequency and severity of symptoms are difficult to interpret and appear to be grounded in very little in the way of empirical data. Details on how we have used this information to estimate short-term health impacts are available at our **2011 deworming report**.

These calculations are highly sensitive to assumptions, especially regarding:

- Adjustments for the limitations of the evidence base for deworming.
- Prevalence of different infections where deworming takes place. We have little information allowing us to separate the effects of different infections.
- Frequency of treatment.

We estimate that deworming programs are in the same range of cost-effectiveness as our other **priority programs**.

Note that our cost-effectiveness analyses are simplified models that do not take into account a number of factors. There are limitations to this kind of cost-effectiveness analysis, and we believe that **cost-effectiveness estimates such as these should not be taken literally**, due to the significant uncertainty around them. We provide these estimates (a) for comparative purposes and (b) because working on them helps us ensure that we are thinking through as many of the relevant issues as possible.

Is there room for more funding in deworming?

We believe there is substantial room to do more deworming in suitable countries. Details at our reviews of the **Schistosomiasis Control Initiative** and the **Deworm the World Initiative**.

Our process

2014

In 2014, we limited our update to searching for RCTs examining the long-term effects of deworming, because we believed that work had the highest chance of impacting our view for the amount of research time invested. We found Croke 2014, discussed the results with Dr. Kevin Croke and published a **blog post** on our findings.

2015

We reviewed two updated papers (**Ozier 2015** and **Baird et al 2015 - November**) on studies we already discuss in the intervention report (**Ozier 2011** and **Baird et al. 2012**). These updated papers reach substantially the same conclusions as the previous papers.[1][12]

We also searched for new, well-identified studies on the long-term effects of deworming. In particular, we searched Google scholar for studies published since 2014 containing the phrase "Croke 2014" under the assumption that new studies on the long-term effects would cite **Croke 2014** and we checked if **Ozier 2015** and **Baird et al 2015 - November** cited any new studies on the long-term effects of deworming. We did not find any new studies.

Giving What We Can raised the question of whether deworming against STH might increase malaria intensity or prevalence.[113] We did a preliminary assessment of the evidence on the effect of deworming on malaria and updated the **section** on "Possible negative/offsetting impact."

We **blogged** about two re-analyses of **Miguel and Kremer 2004** and an updated Cochrane review on deworming published in 2015. These studies did not substantively change our conclusions.

2017

We updated this page to include analyses that we had conducted on deworming since our last intervention report update, such as Senior Advisor David Roodman's blog posts covering his overall assessment of the evidence (**here** and **here**), updated views on **Croke 2014** (discussed **above**), and Roodman's reanalysis of **Bleakley 2007** (**here**).

We briefly reviewed other potentially relevant papers that we became aware of since our last intervention report update. We discussed some relevant new papers above but deprioritized deeply reviewing several individual papers because they seemed unlikely to meaningfully update our view of the intervention. For details on papers we deprioritized, see **GiveWell, 2017 review of deworming literature: deprioritized papers**. To learn about potentially relevant papers, we have set up Google Scholar alerts so that we are notified when new studies cite the key papers discussed in this intervention report (e.g. **Miguel and Kremer 2004**, **Baird et al. 2016**, and **Taylor-Robinson et al. 2015**). We also learn about relevant research papers through a variety of other channels, including speaking with researchers and charities focused on deworming.

We updated the **"impacts on general health" section** of this report to reflect the conclusions from Roodman's recent analysis and recently published systematic reviews.

We also reviewed our deworming cost-effectiveness analysis and provided more detailed explanations for several inputs; see the most recent version of **our core cost-effectiveness model**.

Sources

Document	Source
Abanyie et al 2013	**Source** (**archive**)
Awasthi et al. 2013	**Source** (**archive**)
Baird 2007 (unpublished dissertation)	Unpublished
Baird et al 2015 - November	**Source** (**archive**)
Baird et al. 2011	**Source** (**archive**)
Baird et al. 2012	**Source**
Baird et al. 2015 - Appendix	**Source** (**archive**)
Baird et al. 2016	**Source** (**archive**)
Baird et al. 2016 - Appendix	**Source** (**archive**)
Beasley et al. 1999	**Source** (**archive**)
Bennett and Guyatt 2000	**Source** (**archive**)
Bleakley 2007	**Source** (**archive**)
Brutus et al 2006	**Source** (**archive**)
Brutus et al 2007	**Source** (**archive**)
Bundy et al. 2004	**Source** (**archive**)
Bundy et al. Intestinal nematode infections	**Source**
Cavalli et al 2010	**Source** (**archive**)

CDC soil-transmitted helminths estimates	**Source** (**archive**)
Charles H King, Professor of International Health at Case Western Reserve University, email to GiveWell, November 10, 2011	**Source**
Croke 2014	**Source** (**archive**)
Danso-Appiah et al. 2008	**Source** (**archive**)
Duflo et al. 2012	**Source** (**archive**)
GiveWell, 2017 review of deworming literature: deprioritized papers	**Source**
GiveWell, Deworming replicability adjustment, "Sensitivity analyses of the deworming effect" section	**Source**
GiveWell. Schistosomiasis mortality analysis	**Source**
GiveWell's non-verbatim summary of a conversation with DeWorm3, February 24, 2016	**Source**
Giving What We Can, An update on the effectiveness of Deworm the World Initiative (DtWI), 2015	**Source** (**archive**)
Gulani et al. 2007	**Source** (**archive**)
Hotez et al. 2006	**Source** (**archive**)
Jullien, Sinclair, and Garner 2016	**Source** (**archive**)
King 2010	**Source** (**archive**)
King and Dangerfield-Cha 2008	**Source** (**archive**)
King, Dickman, and Tisch 2005	**Source** (**archive**)
Kinung'hi et al 2015	**Source** (**archive**)
Kirwan et al 2010	**Source** (**archive**)
Kramer et al. 2014	**Source** (**archive**)

Kremer and Miguel 2007	**Source** (**archive**)
Lengeler 2004	**Source** (**archive**)
Lo et al. 2015	**Source** (**archive**)
Mathers, Ezzati, and Lopez 2007	**Source** (**archive**)
Mathers, Lopez, and Murray 2006	**Source** (**archive**)
Miguel and Kremer 2004	**Source** (**archive**)
Murray, Murray, Murray and Murray 1978	**Source** (**archive**)
Nacher 2011	**Source** (**archive**)
Nacher 2011, Additional file 1	**Source** (**archive**)
National Institutes of Health. Vomiting blood	**Source** (**archive**)
Ndibazza et al. 2012	**Source** (**archive**)
Olds et al 1999	**Source** (**archive**)
Ouma et al. 2005	**Source** (**archive**)
Ozier 2011	**Source** (**archive**)
Ozier 2015	**Source** (**archive**)
Roodman 2017, comment on Jullien, Sinclair, and Garner 2016	**Source** (**archive**)
Roodman 2017, replication and reanalysis of Bleakley 2007	**Source**
Saconato and Atallah 2009	**Source** (**archive**)

Salazar-Castanon, Legorreta-Herrera and Rodriguez-Sosa 2014	**Source** (**archive**)
Smith and Brooker 2010	**Source** (**archive**)
Sommer, West, and Martorell 2013	**Source** (**archive**)
Stephenson et al. 1985a	**Source** (**archive**)
Stephenson et al. 1985b	**Source** (**archive**)
Taylor-Robinson et al. 2012	**Source** (**archive**)
Taylor-Robinson et al. 2015	**Source** (**archive**)
Taylor-Robinson, Jones, and Garner 2007	**Source** (**archive**)
The Times of India 2012	**Source** (**archive**)
Van der Werf and de Vlas 2001	**Source**
Van der Werf et al. 2003	**Source** (**archive**)
Vercruysse et al. 2011	**Source** (**archive**)
Vercruysse, Levecke, and Prichard 2012	**Source** (**archive**)
Welch et al. 2017	**Source** (**archive**)
Wiria et al 2013	**Source** (**archive**)
Wiria et al 2013, Appendix S1	**Source** (**archive**)
World Health Organization. Global Burden of Disease 2004: Deaths by Age, Sex, and Cause for the year 2004	**Source**
World Health Organization. Preventive chemotherapy in human helminthiasis	**Source** (**archive**)

World Health Organization. Schistosomiasis fact sheet	**Source** (**archive**)
World Health Organization. The global burden of disease: 2004 update	**Source**
World Health Organization. Worldwide prevalence of anaemia 1993–2005: WHO global database on anaemia	**Source** (**archive**)

Supplementary Sources

Document	Source
GiveWell. New Cochrane Review of the Effectiveness of Deworming	**Source**
King, Charles H. 2011. Schistosomiasis: challenges and opportunities	**Source** (**archive**)
Stephenson, L.S., et al. 1989. Single dose metrifonate or praziquantel treatment in Kenyan children. II. Effects on growth in relation to Schistosoma haematobium and hookworm egg counts	**Source** (**archive**)
World Health Organization. Schistosomiasis strategy	**Source** (**archive**)

1. "People become infected when larval forms of the parasite – released by freshwater snails – penetrate their skin during contact with infested water.... There are two major forms of schistosomiasis – intestinal and urogenital – caused by five main species of blood fluke (see table)." **World Health Organization. Schistosomiasis fact sheet**

2. **King and Dangerfield-Cha 2008**, Pg 67.

3. **King, Dickman, and Tisch 2005**, Pg 1564.

4. - **King and Dangerfield-Cha 2008**, Pg 67.
   - **King 2010**, Pg 3.

5. "I do think that the same effects [as with S. japonicum, the strain in the Coutinho et al. 2006 study,] obtain with S. mansoni and S. haematobium. It is possible that their effect size will be smaller than that seen with S. japonicum—there is a school of thought which suggests that anti-S. japonicum inflammation is more intense because of its higher egg output and its more recent switch to parasitism of the human host. I don't know if this is true." **Charles H King, Professor of International Health at Case Western Reserve University, email to GiveWell, November 10, 2011**.

6. **Saconato and Atallah 2009** Pg 2.

7. **Danso-Appiah et al. 2008**, Pg 2.

8. "The age-dependent patterns of infection prevalence are generally similar among the major helminth species, exhibiting a rise in childhood to a relatively stable asymptote in adulthood (figure 24.1). Maximum prevalence of A. lumbricoides and T. trichiura is usually attained before five years of age, and the maximum prevalence of hookworm and schistosome infections is usually attained in adolescence or in early adulthood. The nonlinear relationship between prevalence and intensity has the consequence that the observed age-prevalence profiles provide little indication of the underlying profiles of age intensity (age in relation to worm burden). Because intensity is linked to morbidity, the age-intensity profiles provide a clearer understanding of which populations are vulnerable to the different helminths (figure 24.1). For A. lumbricoides and T. trichiura infections, the age-intensity profiles are typically convex in form, with the highest intensities in children 5 to 15 years of age (Bundy 1995). For schistosomiasis, a convex pattern is also observed, with a similar peak but with a plateau in adolescents and young adults 15 to 29 years of age (Kabatereine and others 1999). In contrast, the age-intensity profile for hookworm exhibits considerable variation, although intensity typically increases with age until adulthood and then plateaus (Brooker, Bethony, and Hotez 2004). In East Asia it is also common to find the highest intensities among the elderly. However, more generally, children and young adults are at higher risk of both harboring higher levels of infection (thus greater levels of morbidity) and becoming reinfected more quickly. Both may occur at vital stages in a child's intellectual and physical development." **Hotez et al. 2006**, Pgs 469-470.

9. "The eggs of S. haematobium have a terminal spine and must traverse the bladder tissues towards the lumen of the bladder and urinary tract for elimination via urine. In the process, a considerable number become trapped in the bladder walls and surrounding tissues to initiate immune- induced inflammatory reactions, which subsequently lead to morbidity. It is important to note that eggs trapped in the tissues cause disease rather than the worms themselves." **Danso-Appiah et al. 2008**, Pg 3.

10.

- "Haematuria (blood in urine) and dysuria (painful urination) are the main early symptoms of the disease." **Danso-Appiah et al. 2008**, Pg 3.
- “At the time of our follow-up examinations, prevalence of hematuria was 40% among the previously treated group and 39% among un- treated subjects (P = not significant). Moderate-to-severe hematuria (visible hematuria = 2+ or 3+ by dipstick) was more common among untreated subjects (prevalence = 24%) than among those previously treated (prevalence = 14%), and this difference had borderline statistical significance (McNemar’s S = 3.6, P = 0.058).” **Ouma et al. 2005**, Pg 361.

11.

"Sustained heavy infection leads to iron deficiency anaemia and other nutritional deficiencies, especially in children (Awasthi 2003; [**King, Dickman, and Tisch 2005**]. The disease often results in retarded growth, reduced physical activity, and impaired cognitive function in children (Stephenson 1993; Nokes 1999; PCD 1999; Jukes 2002; WHO 2002)." **Danso-Appiah et al. 2008**, Pg 3.

12.

"Late-stage complications are insidious and include calcification of the bladder wall, bladder stones, and secondary bacterial infection (Jordan 1993). Tissue damage caused by trapped eggs can lead to diffuse or localized wall thickening of the bladder and the distal ureter hydronephrosis orhydroureter, which may eventually lead to kidney failure (Kardorff 2001; WHO 2002; **Van der Werf et al. 2003**). Elevated urine albumin levels and reported pain upon micturition by children have a strong correlation with S. haematobium infection (Rollinson 2005). An important long-term consequence of infection is squamous cell carcinoma of the bladder (Jordan 1993; King 2005; Shiff 2006). A recent review points out that bladder carcinoma is the seventh most common cancer worldwide in men and that the highest incidence rate among men is found in Egypt (37.1 per 100,000 person-years) (Murta-Nascimento 2007), which might be related to S. haematobium infection and morbidity (Jordan 2000)." **Danso-Appiah et al. 2008**, Pg 3.

13.

"Schistosomiasis infects the intestine, liver, and spleen. It can cause bloody diarrhoea, bloody stools, and abdominal pain (Gryseels 1992; WHO 1993). Infection of the liver and spleen causes liver fibrosis and portal hypertension that are generally irreversible in the late stages and kill patients, sometimes as a result of haemorrhage from varices (WHO 1993). Liver failure may also occur, especially when S. mansoni infection is associated with viral hepatitis (Pereira 1994)." **Saconato and Atallah 2009**, Pg 2.

14.

There is substantial disagreement about the number of annual fatalities due to schistosomiasis-caused non-functioning kidneys and hematemesis (estimates range from under 27,000 to 280,000).

"WHO (2002) estimates that 27,000 people die annually from STH infections and schistosomiasis (case fatality rate of 0.0014 percent). Many investigators, however, believe that this figure is an underestimate. Crompton (1999) estimated that 155,000 deaths annually occur from these infections (case fatality rate of 0.08 percent), whereas Van der Werf et al. (2003), using the limited data available from Africa, estimated the schistosomiasis mortality alone at 280,000 per year (case fatality rate of 0.014 percent) because of nonfunctioning kidneys (from S. haematobium) and hematemesis (from S. mansoni). Therefore, the difference between estimates for helminth-associated mortality is more than 10-fold." **Hotez et al. 2006**, Pg 470.

15.

“Schistosomiasis is, in its very essence, a chronic inflammatory disease. This is because parasite eggs must pass through host tissues from the circulation to the lumen of bowel or bladder in order to leave the human body. However, this is an inefficient process — during the course of infection, over half of the eggs produced by female schistosomes never leave the human body and remain trapped in host tissues. There, the eggs induce a granulomatous response that progresses to focal areas of fibrosis within the affected organ. Over many years, the cumulative impact of tissue damage can lead to organ failure and consequent severe clinical morbidity and mortality. Early in infection, some of the tissue damage is reversible, but as fibrosis progresses,

the cumulative damage caused by infection becomes irreversible. Even when infection is over, which may occur as adults reach their 30s and 40s, irreversible parasite-mediated organ damage may continue to affect patient health status." **King and Dangerfield-Cha 2008**, Pg 67.

16. **CDC soil-transmitted helminths estimates**.

17. "A. lumbricoides is the large roundworm (15 cm) and lies free in the human duodenum where it feeds on lumenal contents (see Crompton, Nesheim & Pawlowski (1989) for further details of the biology of this parasite). Like all the other nematodes considered here, the worms are dioecious, which is to say that they exist as male and female. The female produces some 100 000 eggs per day which pass out in the faeces of the host and embryonate externally at a rate determined by local environmental factors. The eggs hatch on ingestion, releasing a larva that undergoes a tissue migration involving the cardiovascular and pulmonary systems. The larva moults as it migrates and ultimately is coughed up from the lungs, swallowed, and becomes established as the adult in the small intestine. The cycle from egg deposition to female patency, when the female is able to produce eggs, has a duration of some 50 days.

    T. trichiura, the human whipworm, is a much smaller worm (25 mm) and inhabits the colon (Bundy & Cooper 1989). The anterior two-thirds of the worm is thin and thread-like and is laced through the mucosal epithelium, upon which the worm is believed to feed, leaving the blunt posterior projecting into the colonic lumen for excretion and oviposition. The female produces some 2000 eggs per day which pass out in the host faeces and embryonate externally. The infectious eggs hatch on ingestion and undergo a specifically local migration, via the crypts of Lieberkühn to the mucosal surface. The development cycle takes some 60 days.

    The two major hookworm species, which are of similar magnitude to the whipworm, inhabit the small intestine, where they attach to villi with biting mouthparts (Schad & Warren 1990). The worms feed on host blood and move frequently to new sites, leaving multiple, bleeding petechial haemorrhages on the mucosal surface." **Bundy et al. 2004**, Pgs 244-45.

18. "Each worm's establishment in a host is the result of a separate infection event, and the number of infective stages shed (the infectiousness of the host) is a function of the number of worms present. In population dynamic terms this implies that the individual worm is the unit of transmission for helminths, while the individual host is the unit for microparasites (Anderson & May 1982)... Since the size of the worm burden varies considerably between individuals, and infection implies only that worms are present, a population of "infected" people will exhibit considerable variation in the severity of disease manifestations." **Bundy et al. 2004**, Pgs 245-46.

19. "The size of the worm burden (the intensity of infection) is therefore a central determinant of helminth transmission dynamics, and is also the major determinant of morbidity since the pathology is related to the size of the worm burden, usually in a non-linear fashion (Stephenson 1987, Cooper & Bundy 1987, 1988). Since the size of the worm burden varies considerably between individuals, and infection implies only that worms are present, a population of "infected" people will exhibit considerable variation in the severity of disease manifestations. The intuitive assumption that all infections are equal may help to explain the historical confusion over the pathogenicity and public health significance of helminth infection (Bundy 1988, Cooper and Bundy 1989). From these considerations it is apparent that an understanding of helminth epidemiology centres around an understanding of the patterns of infection intensity." **Bundy et al. 2004**, Pgs 245-46.

20. **Gulani et al. 2007**.

21.

"There is a general acceptance of the simple view that very intense infection results in illness, a view that reflects both clinical experience of overwhelming infection and, perhaps equally importantly, an atavistic repugnance at the insidious invasion of the body by large numbers of worms. Such extremes of infection result in the severe anaemia of necatoriasis and the intestinal obstruction of ascariasis (Stephenson 1987), and the chronic colitis of classical trichuris dysentery syndrome (Cooper & Bundy 1988)." **Bundy et al. 2004**, Pg 248.

22.

"There is a general acceptance of the simple view that very intense infection results in illness, a view that reflects both clinical experience of overwhelming infection and, perhaps equally importantly, an atavistic repugnance at the insidious invasion of the body by large numbers of worms. Such extremes of infection result in the severe anaemia of necatoriasis and the intestinal obstruction of ascariasis (Stephenson 1987), and the chronic colitis of classical trichuris dysentery syndrome (Cooper & Bundy 1988)." **Bundy et al. 2004**, Pg 248.

23.

"Ascariasis is the best documented helminthiasis in terms of mortality. There are numerous studies of case fatality rates in hospitals (reviewed by Pawlowski & Davies 1989). These indicate that the outcome of acute complications of ascariasis is modified by the general health status of the patient, the intensity of infection and the medical procedure (see Pawlowski & Davies 1989). In one hospital in Sao Paulo, for example, the case fatality rate was 1.35 per cent for conditions which could be managed conservatively, and 26.1 per cent in patients undergoing surgery (Okumura et al. 1974). These studies confirm that death is a not infrequent outcome of complications of ascariasis, but provide little insight into mortality rates in the community. An extrapolation from central hospital data in Myanmar suggests there are 0.008 deaths per 1000 infections per year (Thein-Hliang 1987), but this is considered to be a considerable underestimate since only a small proportion of children with severe complications are likely to have access to the hospital (Pawlowski & Davies 1989). Only two population based estimates are available: one for the Darmstadt epidemic (0.1 deaths per 1000 infected per year) (Krey 1949) and one for Japan prior to national control efforts (0.061 deaths per 1000 infected per year) (Yokogawa 1976). Based on the present estimate of global infection, these rates suggest that between 8 000 and 14 000 children die each year.

The final estimate of global mortality due to ascariasis in the Global Burden of Disease project was 11,000 concentrated in the age group 5–14 years (Murray and Lopez 1996). Mortality was distributed by region in proportion to the region-specific population at risk (above higher threshold) and to the region-specific probability of dying between birth and 4 years (World Bank 1993). This last quantity was added to take account of regional variations in access to acute medical services.

No population-based mortality estimates have been published for T. trichiura infection. Prior to the advent of safe and effective therapy for T. trichiura infection in the late 1970s a number of reports described paediatric inpatients with Trichuris Dysentery Syndrome who, despite clinical efforts, died as a result of profuse haemorrhage and secondary anaemia (Wong and Tan 1961, Fisher and Cremin 1970) or of intussusception (Reeder, Astacio & Theros 1968). Although there continue to be reports of the syndrome, a fatal outcome in a clinical setting today would suggest inappropriate management. The picture in the community, however, may be rather different since, in the absence of specific diagnosis, the aetiology of chronic bloody dysentery may be unrecognized. Nevertheless, mortality is undoubtedly a rare consequence of trichuriasis.

The profound anaemia of hookworm infection is life-threatening and has been estimated, although the means of estimation are not described, to result in 65 000 deaths per year (World Health Organization 1992). Again there is a lack of empirical data, presumably in this case because of the difficulty in identifying the etiology of anaemia-related deaths. A figure of 4 300 deaths was used by Murray and Lopez (1996) and was distributed to ascribe the highest proportion of mortality to women of childbearing age (15–44 years) and to older age groups. The distribution of deaths between regions was divided in the same way as for the other infections.

In including these estimates of mortality we recognize that they are unsupported by vital registration statistics. But it should also be recognized that intense infection is most prevalent in the poorest regions of the poorest countries. In such areas

mortality may be most likely because of limited access to appropriate management, while both the diagnosis of cause of death and its registration may be least reliable. There is clear evidence that deaths do occur. What is unclear is the extent of this mortality." **Bundy et al. 2004**, Pgs 281-82.

24. **World Health Organization. Preventive chemotherapy in human helminthiasis**, Pg 10.

25. **World Health Organization. Preventive chemotherapy in human helminthiasis**, Pg 10.

26. **World Health Organization. Preventive chemotherapy in human helminthiasis**, Pg 41.

27. "Schools offer a readily available, extensive, and sustained infrastructure with a skilled workforce that is in close contact with the community. With support from the local health system, teachers can deliver the drugs safely. Teachers need only a few hours of training to understand the rationale for deworming and to learn how to give out the pills and keep a record of their distribution." **Hotez et al. 2006**, Pg 473.

28.
- **Danso-Appiah et al. 2008**.
- **Saconato and Atallah 2009**.

29. "The CRs [cure rates] and ERRs [egg reduction rates] for the recommended doses of albendazole and mebendazole in treating A. lumbricoides, T. trichiura and hookworm are shown in Fig. 1. For A. lumbricoides, all drug regimens are highly effective, with median CRs of 95–97% and median ERRs of 99–100%. More importantly, there is little variation in the drug efficacies between the individual studies for any given drug regimen. In contrast, the patterns for T. trichiura and hookworm are more variable. For both of these parasites, there is marked heterogeneity both in the drug efficacy between drug regimens and the drug efficacy between individual studies administering a given regimen. This is particularly evident for T. trichiura, for which both single-dose albendazole and mebendazole show poor levels of drug efficacy, particularly in terms of CR. For example, the median CR for a single dose of 400 mg albendazole is only 38%, with individual studies reporting CRs ranging from 4.9% to 99.3%." **Bennett and Guyatt 2000**, Pg 72.

30. **World Health Organization. Worldwide prevalence of anaemia 1993–2005: WHO global database on anaemia**. See Table 2.1 (page 4) for haemoglobin thresholds by age.

31. See the "Haemoglobin levels" section in **our previous review**.

32.
- See the previous version of our deworming intervention report that discusses impacts on haemoglobin levels **here**. **Taylor-Robinson et al. 2015** and **Kramer et al. 2014**, the updated versions of **Taylor-Robinson et al. 2012** and **Danso-Appiah et al. 2008** respectively, were released after we last conducted a detailed review of the evidence for the effect of deworming on anemia. We believe that these new systematic reviews include new studies that make our previous analysis outdated, but we have not yet reviewed each study in the previous analysis and compared them with the studies included in the new meta-analyses to determine precisely what changed. We also have not revisited the conclusions from **Smith and Brooker 2010**, a meta-analysis of combination deworming discussed in a **previous** version of our deworming intervention report.
- Haemoglobin is a proxy for anemia. **Taylor-Robinson et al. 2015**, a Cochrane meta-analysis of the effects of STH deworming, concludes:

"Treating children known to be infected

Treating children known to be infected with a single dose of deworming drugs (selected by screening, or living in areas where all children are infected) may increase weight gain over the next one to six months (627 participants, five trials, low quality evidence). The effect size varied across trials from an additional 0.2 kg gain to 1.3 kg. There is currently insufficient evidence to know whether treatment has additional effects on haemoglobin (247 participants, two trials, very low quality evidence); school attendance (0 trials); cognitive functioning (103 participants, two trials, very low quality evidence), or physical well-being (280 participants, three trials, very low quality evidence).

Community deworming programmes

Treating all children living in endemic areas with a dose of deworming drugs probably has little or no effect on average weight gain (MD 0.04 kg less, 95% CI 0.11 kg less to 0.04 kg more; trials 2719 participants, seven trials, moderate quality evidence), even in settings with high prevalence of infection (290 participants, two trials). A single dose also probably has no effect on average haemoglobin (MD 0.06 g/dL, 95% CI -0.05 lower to 0.17 higher; 1005 participants, three trials, moderate quality evidence), or average cognition (1361 participants, two trials, low quality evidence)." **Taylor-Robinson et al. 2015**, Pg. 2.

- **Kramer et al. 2014**, a Cochrane meta-analysis of drugs for treating urinary schistosomiasis (an update to **Danso-Appiah et al. 2008**, a previous meta-analysis we relied on for estimating the effect of deworming on anemia), finds no effect of a single dose of praziquantel on haemoglobin, a small non-statistically significant effect of a single dose of metrifonate on haemoglobin, and a small statistically significant effect of multiple doses of metrifonate on haemoglobin. See Analyses 1.3 (Pg. 91), 6.2 (Pg. 116), and 7.2 (Pg. 118) in **Kramer et al. 2014** for details.

33.

- A **previous version of our deworming intervention report** details the evidence for the potential effect of deworming on anemia, and it concludes that the evidence is mixed. **Taylor-Robinson et al. 2015** and **Kramer et al. 2014** were released after we last conducted a detailed review of the evidence for the effect of deworming on anemia. We believe that these new systematic reviews include new studies that make our previous analysis outdated, but we have not yet reviewed each study in the previous analysis and compared them with the studies included in the new meta-analyses to determine precisely what changed.
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34.

- "Main results

We identified 45 trials, including nine cluster-RCTs, that met the inclusion criteria. One trial evaluating mortality included over one million children, and the remaining 44 trials included a total of 67,672 participants. Eight trials were in children known to be infected, and 37 trials were carried out in endemic areas, including areas of high (15 trials), moderate (12 trials), and low prevalence (10 trials).

Treating children known to be infected

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Similiarly, regularly treating all children in endemic areas with deworming drugs, given every three to six months, may have little or no effect on average weight gain (MD 0.08 kg, 95% CI 0.11 kg less to 0.27 kg more; 38,392 participants, 10 trials, low quality evidence). The effects were variable across trials; one trial from a low prevalence setting carried out in 1995 found an increase in weight, but nine trials carried out since then found no effect, including five from moderate and high prevalence areas.

There is also reasonable evidence that regular treatment probably has no effect on average height (MD 0.02 cm higher, 95% CI 0.14 lower to 0.17 cm higher; 7057 participants, seven trials, moderate quality evidence); average haemoglobin (MD 0.02 g/dL lower; 95% CI 0.08 g/dL lower to 0.04 g/dL higher; 3595 participants, seven trials, low quality evidence); formal tests of cognition (32,486 participants, five trials, moderate quality evidence); exam performance (32,659 participants, two trials, moderate quality evidence); or mortality (1,005,135 participants, three trials, low quality evidence). There is very limited evidence assessing an effect on school attendance and the findings are inconsistent, and at risk of bias (mean attendance 2% higher, 95% CI 4% lower to 8% higher; 20,243 participants, two trials, very low quality evidence).
In a sensitivity analysis that only included trials with adequate allocation concealment, there was no evidence of any effect for the main outcomes.

Authors' conclusions

Treating children known to have worm infection may have some nutritional benefits for the individual. However, in mass treatment of all children in endemic areas, there is now substantial evidence that this does not improve average nutritional status, haemoglobin, cognition, school performance, or survival." **Taylor-Robinson et al. 2015**, Abstract.

- "We included 52 studies of duration 5 years or less with 1 108 541 children, and four long-term studies 8–10 years after mass deworming programmes with more than 160 000 children. Overall risk of bias was moderate. Mass deworming for soil-transmitted helminths compared with controls led to little to no improvement in weight over a period of about 12 months (0·99 kg, 95% credible interval [CrI] −0·09 to 0·28; moderate certainty evidence) or height (0·07 cm, 95% CrI −0·10 to 0·24; moderate certainty evidence), little to no difference in proportion stunted (eight fewer per 1000 children, 95% CrI −48 to 32; high certainty evidence), cognition measured by short-term attention (−0·23 points on a 100 point scale, 95% CI −0·56 to 0·14; high certainty evidence), school attendance (1% higher, 95% CI −1 to 3; high certainty evidence), or mortality (one fewer per 1000 children, 95% CI −3 to 1; high certainty evidence). We found no data on quality of life and little evidence of adverse effects. Mass deworming for schistosomiasis might slightly increase weight (0·41 kg, 95% CrI −0·20 to 0·91) and has little to no effect on height (low certainty evidence) and cognition (moderate certainty evidence). Our analyses do not suggest indirect benefits for untreated children from being exposed to treated children in the community. We are uncertain about effects on long-term economic productivity (hours worked), cognition, literacy, and school enrolment owing to very low certainty evidence. Results were consistent across sensitivity and subgroup analyses by age, worm prevalence, baseline nutritional status, infection status, impact on worms, infection intensity, types of worms (ascaris, hookworm, or trichuris), risk of bias, cluster versus individual trials, compliance, and attrition." **Welch et al. 2017**, Abstract.

35.

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36.

We primarily refer here to **Van der Werf and de Vlas 2001**, the working paper version (with more detail) than **Van der Werf et al. 2003**.

37.

Van der Werf and de Vlas 2001, Pgs 3-5.

38.

Van der Werf and de Vlas 2001, Pgs 13-15 discusses the method of generating estimates of the relationship between schistosomiasis prevalence and the prevalence of the various sequelae discussed. Charts throughout the remainder of the review show the curve that is fitted to the data points provided by the studies reviewed. We find that the attribution method

(a) ignores the possibility of confounders, i.e., the possibility that non-schistosomiasis factors (such as poverty and general hygiene) are correlated both with schistosomiasis and with the sequelae discussed; (b) is prone to exaggerate the strength of any given relationship (as we believe can be seen by examining the charts).

39. **Van der Werf et al. 2003**, Pg 132.

40. **World Health Organization. The global burden of disease: 2004 update**, Pg 110.

41. "Van der Werf MJ, de Vlas SJ. Morbidity and infection with schistosomes or soil-transmitted helminths. Rotterdam, Erasmus University, 2001." **World Health Organization. The global burden of disease: 2004 update**, Pg 139.

42. One of the most severe symptoms discussed is severe hematemesis (vomiting blood). But Van der Werf et al. rely on self-reported survey data of hematemesis, (**Van der Werf and de Vlas 2001**, Pgs 62-63) which is problematic because vomiting blood can easily be confused with coughing blood or even a nosebleed (**National Institutes of Health. Vomiting blood**).

43.
- "The course of a schistosome infection complicates the prediction of mortality figures. Often there is a long interval between infection and death, most patients that will die of schistosomiasis die more than 10 years after the initial infection. Only a few people will die during or just after the invasion stage of the infection (Katayama fever). Another complicating factor is that the direct cause of death is liver failure or hematemesis. These sequelae can also be induced by other causes, which are prevalent in countries endemic for schistosomiasis, such as hepatitis B infection or excessive alcohol use. Both the long time span between initial infection and mortality and the aspecific direct cause of death complicate the predictions of mortality." **Van der Werf and de Vlas 2001**, Pg 65.
- "The GBD 2002 estimated that schistosomiasis was responsible for around 15,000 deaths globally (excluding attributable cancer deaths), although others have argued that the figure should be much higher. [**Van der Werf and de Vlas 2001**], using limited data from Africa, estimated that schistosomiasis caused 210,000 deaths annually. A literature review found limited data from studies with small sample sizes, limiting ability to extrapolate to population level. In the absence of usable studies, a back-calculation method was employed to estimate approximate case fatality rates for two populations with significant numbers of schistosomiasis deaths recorded in death registration data ... [the] revised global estimate for deaths due to schistosomiasis (excluding cancers caused by schistosomiasis) [is] 41,000 for 2004." **World Health Organization. The global burden of disease: 2004 update**, Pg 110.

44. **World Health Organization. The global burden of disease: 2004 update**, Pg 110.

45. “Estimated total malaria deaths for 2004 were 0.89 million, of which 771 000 were in children aged under five years. These estimates are lower than those in the GBD 2002 (1.27 million deaths, of which 1.15 million deaths were of children aged under five years).” **World Health Organization. The global burden of disease: 2004 update**, Pg 109.

46. **GiveWell. Schistosomiasis mortality analysis** "YLL per DALY" rows on "From GBD" sheet. For more on these terms, see our **discussion of DALYs**.

47. **Bundy et al. 2004**, Pgs 269-273.

48.

- "There are also more serious consequences of infection, largely associated with obstruction of ducts and intestinal lumen by these large worms. Systematic data on these acute complications are lacking, but the numerous reports based on inpatient records suggest that ascariasis is an important cause of hospitalization in endemic areas (reviewed by Pawlowski & Davies 1989). Ascariasis was the cause of 2.6 per cent of all hospital admissions in Kenya in 1976, and 3 per cent in a children's hospital in Myanmar between 1981 and 1983 (Stephenson, Lathan & Oduori 1980, Thein-Hlaing 1987). Complications resulting from ascariasis accounted for 0.6 per cent of all admissions to a paediatric surgery department in South Africa in 1987, 5.8 per cent of emergency admissions to a hospital in Mexico in 1975, 10.6 per cent of admissions for acute abdominal emergency to a children's hospital in Myanmar, and between 0.8 and 2.5 per cent of admissions in a survey of hospitals in China (Flores & Reynaga 1978, World Health Organization 1987, Thein-Hlaing et al. 1990). The most common abdominal emergencies presenting are intestinal obstruction and biliary ascariasis, the proportions varying geographically, perhaps because of differences in diagnostic procedures (Maki 1972). The classical surgical presentation is in patients between 3 and 10 years of age, although adults also may be affected (Davies and Rode 1982, Chai et al. 1991). Laparotomy attributable to ascariasis was the second most common cause of all laparotomies in 2–4 year old children in Durban, Lishiu and Sao Paulo, and the fifth or sixth cause in adults in Myanmar, China and Nigeria (World Health Organization 1987). Reports using unstandardized indicators indicate that between 0.02 and 0.9 per cent of infections may require hospitalization (Pawlowski & Davies 1989), the proportion presumably varying with the local intensity of infection. Thus of the 4.5 per cent of infected children under 10 years of age who are here estimated to exceed the higher threshold of infection, between 0.4 and 20 per cent are likely to require hospitalization. These children will suffer a severely disabling condition, which may be life-threatening (see below), but which can be alleviated by appropriate clinical management. If it is assumed that such cases are managed appropriately, then the duration of disability is likely to be a few weeks. Complicated ascariasis has a reported history of over 10 days followed by 5 days of management, while the management of biliary ascariasis involves 4–6 weeks of observation before opting for surgical intervention (Davies & Rode 1982). The disability therefore is considered, for the present analyses, to be contemporaneous with infection, to have a duration of 4 weeks, to have a severity of Class III (Murray & Lopez 1996), and to affect 5 per cent of children under 15 years of age with burdens exceeding the higher threshold. Note that this is a conservative assumption since it excludes the documented, though rare, occurrence of complications in adults. Furthermore, the case rates for children are based on records from tertiary facilities to which a substantial proportion of the most disadvantaged and heavily infected children may have limited access." **Bundy et al. 2004**, Pgs 269-270.
- "[Mortality] is the weakest area of DALY estimation because of the lack of empirical data. Ascariasis is the best documented helminthiasis in terms of mortality. There are numerous studies of case fatality rates in hospitals (reviewed by Pawlowski & Davies 1989). These indicate that the outcome of acute complications of ascariasis is modified by the general health status of the patient, the intensity of infection and the medical procedure (see Pawlowski & Davies 1989). In one hospital in Sao Paulo, for example, the case fatality rate was 1.35 per cent for conditions which could be managed conservatively, and 26.1 per cent in patients undergoing surgery (Okumura et al. 1974). These studies confirm that death is a not infrequent outcome of complications of ascariasis, but provide little insight into mortality rates in the community. An extrapolation from central hospital data in Myanmar suggests there are 0.008 deaths per 1000 infections per year (Thein-Hliang 1987), but this is considered to be a considerable underestimate since only a small proportion of children with severe complications are likely to have access to the hospital (Pawlowski & Davies 1989). Only two population based estimates are available: one for the Darmstadt epidemic (0.1 deaths per 1000 infected per year) (Krey 1949) and one for Japan prior to national control efforts (0.061 deaths per 1000 infected per year) (Yokogawa 1976). Based on the present estimate of global infection, these rates suggest that between 8 000 and 14 000 children die each year.
  The final estimate of global mortality due to ascariasis in the Global Burden of Disease project was 11 000 concentrated in the age group 5–14 years (Murray and Lopez 1996). Mortality was distributed by region in proportion to the region-specific population at risk (above higher threshold) and to the region-specific probability of dying between birth and 4 years (World Bank 1993). This last quantity was added to take account of regional variations in access to acute medical services."**Bundy et al. 2004**, Pgs 281-282.

49.

- "The disability therefore is considered, for the present analyses, to be contemporaneous with infection, to have a duration of 4 weeks, to have a severity of Class III (Murray & Lopez 1996), and to affect 5 per cent of children under 15 years of age with burdens exceeding the higher threshold." **Bundy et al. 2004**, Pgs 269-270.
- Table 9.9 reports that 525 per 100,000 5-14 year olds in Sub-Saharan Africa have worm burdens exceeding the higher threshold. **Bundy et al. 2004**, Pg 268.
- 5% of 525 per 100,000 is 0.0002625.

50.

Unfortunately, the published version (**Bundy et al. 2004**) does not contain regionally disambiguated mortality estimates, so we use the figure from the **unpublished working paper** that was used to generate the DCP's cost-effectiveness estimate, of .3 per 100,000 population. **Bundy et al. Intestinal nematode infections**, Table 9, Pg 72.

51.

"Particularly large burdens of T. trichiura may result in the "classical" dysenteric form of trichuriasis, synonymous with Trichuris Dysentery Syndrome (Ramsey 1962) and Massive Infantile Trichuriasis (Kouri & Valdes Diaz 1952). This typically occurs in children between 3 and 10 years of age and is associated with burdens involving at least several hundreds of worms carpeting the colonic mucosa from ileum to rectum. The colon is inflamed, oedematous and friable, and often bleeds freely (Venugopal et al. 1987). Reviews of case histories suggest that the mean duration of disease at the time of presentation is typically in excess of 12 months and that relapse after treatment frequently occurs (Gilman et al. 1983, Cooper et al. 1990, Callender et al. 1994). The probability of relapse, and of a child experiencing multiple episodes, is greatly enhanced because a proportion of heavily infected children are predisposed to reacquire heavy infection even after successful treatment (Bundy et al. 1987a, 1987b). The typical signs of the syndrome (see Bundy & Cooper 1989a for a review of 13 studies involving 697 patients) are rectal prolapse, tenesmus, bloody mucoid stools (over months or years), growth stunting, and a profound anaemia, which may lead to a secondary anaemia. The complete spectrum of clinical features associated with the syndrome occurs in some 30 per cent of children with intense trichuriasis. Many of the major clinical effects are reversible by appropriate therapy (Cooper, Bundy & Henry 1986, Gilman et al. 1983), hence the disability is considered here to be a contemporaneous consequence of infection." **Bundy et al. 2004**, Pgs 271-273.

52.

- "For the present analyses it is assumed that the disability is contemporaneous with infection, has a duration of over 12 months, has a severity of Class II (Murray & Lopez, 1996), and affects 20 per cent of children under 15 years of age experiencing the higher threshold of intensity." **Bundy et al. 2004**, Pg 273.
- In Sub-Saharan Africa, 680 per 100,000 school-aged children have worm burdens above the higher threshold of intensity. **Bundy et al. 2004**, Table 9.10, Pg 270.
- 20% of 680 per 100,000 is 0.00136.

53.

"No population-based mortality estimates have been published for T. trichiura infection. Prior to the advent of safe and effective therapy for T. trichiura infection in the late 1970s a number of reports described paediatric inpatients with Trichuris Dysentery Syndrome who, despite clinical efforts, died as a result of profuse haemorrhage and secondary anaemia (Wong and Tan 1961, Fisher and Cremin 1970) or of intussusception (Reeder, Astacio & Theros 1968). Although there continue to be reports of the syndrome, a fatal outcome in a clinical setting today would suggest inappropriate management. The picture in the community, however, may be rather different since, in the absence of specific diagnosis, the aetiology of chronic bloody dysentery may be unrecognized. Nevertheless, mortality is undoubtedly a rare consequence of trichuriasis." **Bundy et al. 2004**, Pg 282.

54.

- "With hookworm the major consequence of infection is anaemia (see Schad & Banwell 1984 and Crompton & Stephenson 1990 for reviews of the extensive literature in this area). Anaemia is associated with: reduced worker productivity; reduced adult and child fitness; reduced fertility in women; reduced intrauterine growth rate, prematurity and low birth weight; and

cognitive deficits (Fleming 1982, Stephenson et al.1993, Pol- litt et al. 1986, Boivin et al. 1993) (Tables 9.12a and 9.12b). Since the higher threshold for the intensity of hookworm infection was selected on the basis of the development of anaemia, it is here assumed that 100 per cent of those exceeding this threshold suffer at least Class I disability. As discussed elsewhere (World Bank 1993), the consequences of anaemia will be more serious for a subset of the affected population, resulting in Class II and Class III disability. The disability weight distribution for anaemia was used for the present analyses, 70 per cent in Class II, 24 per cent in Class III and 6 per cent in Class IV." **Bundy et al. 2004**, Pg 273.

- "The profound anaemia of hookworm infection is life-threatening and has been estimated, although the means of estimation are not described, to result in 65 000 deaths per year (World Health Organization 1992). Again there is a lack of empirical data, presumably in this case because of the difficulty in identifying the etiology of anaemia-related deaths. A figure of 4 300 deaths was used by Murray and Lopez (1996) and was distributed to ascribe the highest proportion of mortality to women of childbearing age (15–44 years) and to older age groups. The distribution of deaths between regions was divided in the same way as for the other infections." **Bundy et al. 2004**, Pg 282.

55.

Mathers, Lopez, and Murray 2006, Pg 162.

56.

World Health Organization. Global Burden of Disease 2004: Deaths by Age, Sex, and Cause for the year 2004, sheet 'AFR', cells G39+G40+G41.

57.

- "Overall child mortality was 5% lower in albendazole than in control blocks, but because randomisation was by block rather than by AWC or by individual this 5% difference is not significant (risk ratio [RR] 0·95, CI 0·88–1·02, p = 0·16). " Pg. 1483.
- Absolute risk of death: Table 3, pg. 1484.
- The sample included 1 million children: "Participants in this cluster-randomised study were children in catchment areas of 8338 ICDS-staffed village child-care centres (under-5 population 1 million) in 72 administrative blocks." Pg. 1478. This generated a sample of 25,582 child deaths. "The 238 remaining duplicates at ages 1·0–6·0 years were eliminated in Oxford by computer matches (199 with the same AWC, sex, first three letters of father's name, and date of death from a disease, 23 with matching for approximate date but closer other similarities, 16 with the same death reported in adjacent AWCs), leaving 25582 child deaths for analysis." Pgs. 1480-1.

58.

"Following World Health Organization recommendations (WHO (1992)), schools with geohelminth prevalence over 50 percent were mass treated with albendazole every six months, and schools with schistosomiasis prevalence over 30 percent were mass treated with praziquantel annually. All treatment schools met the geohelminth cut-off in both 1998 and 1999. Six of twenty-five treatment schools met the schistosomiasis cut-off in 1998 and sixteen of fifty treatment schools met the cut-off in 1999." **Miguel and Kremer 2004**, Pgs. 168-169.

59.

- Note: **Baird et al. 2016** is the most recent version of the relevant paper. In our footnotes, we cite **Baird et al. 2011**, a working paper version of this study. We have confirmed that **Baird et al. 2016** reaches substantially the same conclusions as the working paper **Baird et al. 2011**.
- "The 75 schools involved in this program were experimentally divided into three groups (Groups 1, 2, and 3) of 25 schools each: the schools were first stratified by administrative sub-unit (zone), listed alphabetically by zone, and were then listed in order of enrollment within each zone, and every third school was assigned to a given program group; supplementary appendix A contains a detailed description of the experimental design. The groups are well-balanced along baseline demographic and educational characteristics, both in terms of mean differences and distributions, where we assess the latter with the Kolmogorov-Smirnov test of the equality of distributions (Table 1). The same balance is also evident among the subsample of respondents currently working for wages (see Supplementary Appendix Table A1)." **Baird et al. 2011**, Pgs. 6-7.

60.

"Intestinal helminths—including hookworm, roundworm, whipworm, and schistosomiasis—infect more than one-quarter of the world's population. Studies in which medical treatment is randomized at the individual level potentially doubly underestimate the benefits of treatment, missing externality benefits to the comparison group from reduced disease transmission, and therefore also underestimating benefits for the treatment group. We evaluate a Kenyan project in which school-based mass treatment with deworming drugs was randomly phased into schools, rather than to individuals, allowing estimation of overall program effects. The program reduced school absenteeism in treatment schools by one-quarter, and was far cheaper than alternative ways of boosting school participation. Deworming substantially improved health and school participation among untreated children in both treatment schools and neighboring schools, and these externalities are large enough to justify fully subsidizing treatment. Yet we do not find evidence that deworming improved academic test scores." **Miguel and Kremer 2004**, Abstract.

61.

- "Group 1 pupils also reported better health outcomes after the first year of deworming treatment: four percent fewer Group 1 pupils reported being sick in the past week, and three percent fewer pupils reported being sick often (these differences are significantly different than zero at 95 percent confi-dence). Group 1 pupils also had significantly better height-for-age—a measure of nutritional status—by early 1999, though weight-for-age was no greater on average." **Miguel and Kremer 2004**, Pg. 174.
- See **Miguel and Kremer 2004**, Table V, Pg. 173 for full results.

62.

- Note: **Baird et al. 2016** is the most recent version of the relevant paper. In our footnotes, we cite **Baird et al. 2011**, a working paper version of this study. We have confirmed that **Baird et al. 2016** reaches substantially the same conclusions as the working paper **Baird et al. 2011**.
- "Children in Group 1 and 2 schools thus were assigned to receive 2.41 more years of deworming than Group 3 children on average (Table 1), and these early beneficiaries are what we call the deworming treatment group below. We focus on a single treatment indicator rather than separating out effects for Group 1 versus Group 2 schools since this simplifies the analysis, and because we find few statistically significant differences between Group 1 and 2 (not shown)." **Baird et al. 2011**, Pg. 7.
- "We focus on the KLPS-2 data, rather than KLPS-1, in this paper since it was collected at a more relevant time point for us to assess adult life outcomes: the majority of sample respondents are adults by 2007-09 (with median age at 22 years as opposed to 18 in KLPS-1), have completed their schooling, many have married, and a growing share are engaging in wage employment or self- employment, as shown graphically in Figure 2." **Baird et al. 2011**, Pg. 10.

63.

- "The question of whether – and how much – child health gains improve adult living standards is of major intellectual interest and public policy importance. We exploit a prospective study of deworming in Kenya that began in 1998, and utilize a new dataset with an effective tracking rate of 83% over a decade, at which point most subjects were 19 to 26 years old. Treatment individuals received two to three more years of deworming than the comparison group. Among those with wage employment, earnings are 21 to 29% higher in the treatment group, hours worked increase by 12%, and work days lost to illness fall by a third. A large share of the earnings gains are explained by sectoral shifts, for instance, through a doubling of manufacturing employment and a drop in casual labor. Small business performance also improves significantly among the self-employed. Total years enrolled in school, test scores and self-reported health improve significantly, suggesting that both education and health gains are plausible channels." **Baird et al. 2011**, Abstract.
- Note: **Baird et al. 2016** is the most recent version of the relevant paper. In our footnotes, we cite **Baird et al. 2011**, a working paper version of this study. We have confirmed that **Baird et al. 2016** reaches substantially the same conclusions as the working paper **Baird et al. 2011**.

64.

- "These labor market gains are accompanied by marked shifts in employment sector for the treatment group, with more than a doubling of well-paid manufacturing jobs (especially among males) and declines in both casual labor and domestic

services employment. Changes in the subsector of employment account for nearly all of the earnings gains in deworming treatment group in a Oaxaca-style decomposition." **Baird et al. 2011**, Pg. 3.

- "The most striking impacts are a large increase in manufacturing work for deworming treatment individuals, with a point estimate of 0.072 (s.e. 0.024, Table 7), signifying a tripling of manufacturing employment overall. The gains among males are particularly pronounced at 0.090 (s.e. 0.030). The two most common types of manufacturing jobs in our sample are in food processing and textiles, with establishments ranging in size from small local corn flour mills up to large blanket factories. On the flip side, casual labor employment falls significantly (-0.038, s.e. 0.018), as does domestic service work for females (-0.174, s.e. 0.110), although this latter effect is only marginally significant." **Baird et al. 2011**, Pg. 16.
- Note: **Baird et al. 2016** is the most recent version of the relevant paper. In our footnotes, we cite **Baird et al. 2011**, a working paper version of this study. We have confirmed that **Baird et al. 2016** reaches substantially the same conclusions as the working paper **Baird et al. 2011**.

65.

- "Deworming treatment individuals consume 0.096 more meals (s.e. 0.028, significant at 99% confidence, Panel C) than the control group, and the externality impact is also large and positive (0.080, s.e. 0.023, 99% confidence). This suggests that deworming led to living standard gains in the full sample." **Baird et al. 2011**, Pg 17.
- "A standard LSMS-style consumption expenditure module was collected for roughly 5% of the KLPS-2 sample during 2007-09, for a total of 254 complete surveys. Such surveys are time-consuming and project budget constraints prevented us from collected a larger number of surveys. Note, too, that such data faces an important limitation in practice since consumption expenditures are best captured at the household level, and thus any productivity gains among KLPS respondents would be “diluted” if other household members do not experience similar gains, making them more difficult to detect in per capita household consumption measures. The data indicate that per capita average consumption levels in the control group are reasonable for rural Kenya, at US$580 (in exchange rate terms, Table 8, Panel C), and that food constitutes roughly 64% of total consumption. The estimated treatment effect for total consumption is near zero and not statistically significant at traditional confidence levels (-$14, s.e. $66), though it is worth noting that the confidence interval is quite large and includes large gains." **Baird et al. 2011**, Pg. 18.
- See Table 8, Pg. 41 of **Baird et al. 2011** for full set of related results.
- Note: **Baird et al. 2016** is the most recent version of the relevant paper. In our footnotes, we cite **Baird et al. 2011**, a working paper version of this study. We have confirmed that **Baird et al. 2016** reaches substantially the same conclusions as the working paper **Baird et al. 2011**.

66.

- "There is evidence that adult health also improved as a result of deworming. Respondent self-reported health (on a normalized 0 to 1 scale) improved by 0.041 (s.e. 0.018, significant at 95% confidence, Table 11, panel A). Many studies have found that self-reported health reliably predicts actual morbidity and mortality even when other known health risk factors are accounted for (Idler and Benyamini 1997, Haddock et al. 2006, Brook et al. 1984). Note that it is somewhat difficult to interpret this impact causally since it may partially reflect health gains driven by the higher adult earnings detailed above, in addition to the direct health benefits of earlier deworming. Yet the fact that there were similar positive and statistically significant impacts on self-reported health in earlier periods, namely, in surveys administered in 1999 before most in sample individuals were working (see Table 11, panel C and Miguel and Kremer 2004), suggests that at least part of the effect is directly due to deworming. In terms of other health outcomes, there is no evidence that deworming improved self- reported happiness or wellbeing or reduced major health shocks. Total health expenditures by the respondent in the last month are significantly higher in the treatment group (91.1 Shillings, s.e. 30.0), suggesting that they may have greater ability or willingness to make health investments, but interpretation is again complicated by the fact that such spending also reflects health needs. Despite the finding that the number of meals consumed is larger for deworming treatment individuals (in Table 8), deworming did not lead to higher body mass index (Table 11, Panel B). Nor are there detectable height gains, and these non-impacts hold even when we restrict attention to younger individuals (those in grades 2-4 in 1998, regression not shown)." **Baird et al. 2011**, Pgs. 22-23. See Pg. 44 for full related results, including height, weight-for-height (body mass index), and health spending.

- Note: **Baird et al. 2016** is the most recent version of the relevant paper. In our footnotes, we cite **Baird et al. 2011**, a working paper version of this study. We have confirmed that **Baird et al. 2016** reaches substantially the same conclusions as the working paper **Baird et al. 2011**.

67.

- "We examine school enrollment and attendance using two different data sources in Table 9. In Panel A, the dependent variable is school enrollment as reported by the respondent in the KLPS-2 survey, which equals one if the individual was enrolled for at least part of a given year. These show consistently positive effects from 1999 to 2007 both on the deworming treatment indicator and the externalities term, and the total increase in school enrollment in treatment relative to control schools over the period is 0.279 years (s.e. 0.147, significant at 90% confidence). Note that there is no treatment effect estimate for 1998 since all students were enrolled at some point in 1998, as a criterion for inclusion in the KLPS sample. The treatment effect estimates are largest during 1999- 2003 before tailing off during 2004-07, as predicted in the optimal educational investment framework above since the current opportunity cost of time is rising relative to the later benefits of schooling as individuals age.

  > The data in Panel B is school participation, namely, being found present in school by survey enumerators on the day of an unannounced school attendance check. This is our most objective measure of actual time spent at school, and was a main outcome measure in Miguel and Kremer (2004). The enrollment measure in Panel A misses much of the attendance variation captured in this measure. However, two important limitations of the school participation data are that it was only collected during 1998-2001, and only at primary schools in the study area; the falling sample size between 1998 to 2001 is mainly driven by students graduating from primary school. School participation rates also rise significantly in the deworming treatment group, by 0.074 (s.e. 0.023) and 0.068 (s.e. 0.023) in 1998 and 1999, respectively, before dropping off somewhat in later years (particularly in 2000). Total school participation gains are 0.129 of a year of schooling (s.e. 0.064, significant at 95% confidence). Given that the school enrollment data misses out on attendance impacts, which are sizeable, a plausible lower bound on the total increase in time spent in school induced by the deworming intervention is the 0.129 gain in school participation from 1998-2001 plus the school enrollment gains from 2002-2007, which works out to 0.304 years of schooling." **Baird et al. 2011**, Pgs. 21-22.

- "Test score performance is another natural way to assess deworming impacts on human capital and skills. While the impact of deworming on primary school academic test score performance in 1999 is positive but not statistically significant (Table 10, Panel B), there is suggestive evidence that the passing rate did improve on the key primary school graduation exam, the Kenya Certificate of Primary Education (point estimate 0.046, s.e. 0.031). There is also some evidence that English vocabulary knowledge (collected during the 2007-09 survey) is somewhat higher in the deworming treatment group (impact of 0.076 standard deviations in a normalized distribution, s.e., 0.055). The mean effect size of the 1999 test score, the indicator for passing the primary school leaving exam, and the English vocabulary score in 2007-09 taken together does yield a normalized point estimate of 0.112 that is statistically significant at 90% confidence (s.e. 0.067), providing suggestive evidence of moderate human capital gains in the treatment group. As expected, there is no effect on the Raven's Matrices cognitive exam, which is designed to capture general intelligence rather than acquired skills (Panel B). While many would argue that nutritional gains in the first few years of life could in fact generate improved cognitive functioning as captured in a Raven's exam – as [**Ozier 2011**] indeed does find among younger siblings of the deworming beneficiaries – it was apparently already 'too late' for such gains among the primary school age children in our study." **Baird et al. 2011**, Pg. 22.
- Note: **Baird et al. 2016** is the most recent version of the relevant paper. In our footnotes, we cite **Baird et al. 2011**, a working paper version of this study. We have confirmed that **Baird et al. 2016** reaches substantially the same conclusions as the working paper **Baird et al. 2011**.

68.

"The most important factor in the econometric identification strategy is the randomized assignment of pupils to deworming treatment through the deworming program. Group 1 schools received free deworming treatment starting in 1998; Group 2 schools began in 1999, while Group 3 schools began receiving treatment in 2001. All school re- ceived treatment from 2001-

2003. Thus in 1998, Group 1 schools were treatment schools, while Group 2 and 3 were comparison schools. In 1999, Group 1 and Group 2 schools were treatment schools and Group 3 schools were control schools. Table 4.1 shows the PSDP treatment schedule. Our sample consists of pupils that were in grades 2-7 in 1998 (primary school goes through grade 8). This variation in group, as well as variation in initial grade, provides us with between zero and six years of treatment for each individual. For example, a Group 1 pupil in grade 2 in 1998 would be assigned six years of treatment, while a Group 3 pupil in grade 6 in 1998 would be assigned only one." **Baird 2007 (unpublished dissertation)**, Pgs. 106-107.

69.

Baird 2007 (unpublished dissertation), Table 4.8, Pg. 138.

70.

"Along with health outcomes we also look at the impact of years of deworming on a number of education and labor market outcomes. Given that we see benefits to health from deworming, we might expect that these gains would translate into educational gains. The education results are shown in Table 4.12. We do see some evidence that deworming treatment decreases your likelihood of dropping out for the overall sample, which is driven by benefits for males and those in low infection areas. Increasing treatment from zero to six years decreases your likelihood of dropping out by 6 percent and is significant at the 10% level. These results are similar to those found by Johnson and Schoeni (2007) for the US, who find that low birth weight (their measure of health status) does not influence results for highest grade attended, but does affect dropout rates. It is interesting that our significant education results are for different sub-groups than our health results. This observation suggests that our education gains are not necessarily being driven by health gains. Overall, we see very little in terms of educational or labor market gains when looking at our overall sample or our sub-samples. The coefficients are generally positive, but insignificant. With our sample still in a very transitional stage with many still in school, and others still moving between school and the labor force, it is hard to draw conclusive results from this evidence. We will have clearer results (or absence ofresults) for the impact of deworming on education and labor force participation once we collect the third round of data." **Baird 2007 (unpublished dissertation)**, Pg. 122.

71.

"We do find consistent negative impacts of deworming on cognitive performance,
although for the most part these results are insignificant and small. Looking at the mean effect result for the entire sample, one finds that increasing treatment by one year decreases, albeit insignificantly, the average cognitive score by 0.005 standard deviations. These negative coefficients may result from the fact that treatment leads more vulnerable pupils to stay in school, pupils who are likely to have lower test scores to begin with." **Baird 2007 (unpublished dissertation)**, Pg. 122.

72.

"Ten years after the intervention, I find large cognitive effects—comparable to between 0.5 and 0.8 years of schooling—for children who were less than one year old when their communities received mass deworming treatment. Because treatment was administered through schools, I also estimate effects among children whose older siblings received the treatment directly; in this subpopulation, effects are nearly twice as large." **Ozier 2015**, Abstract.

73.

"The NGO we worked with has a policy of using community cost-recovery in its projects to promote sustainability and confer project ownership on beneficiaries. In the case of deworming, the NGO temporarily waived this policy initially and then planned to phase it in gradually. The fifty Group 1 and Group 2 schools were stratified by treatment group and geographic location and then twenty-five were randomly selected (using a computer random number generator) to pay user fees for medical treatment in 2001, while the other twenty-five continued to receive free medical treatment that year; all Group 3 schools received free treatment in 2001. The deworming fee was set on a per-family basis like most Kenyan primary school fees at the time. This introduced within-school variation in the per-child cost of deworming since households have different numbers of primary school children, variation that we also use to estimate the effect of price on drug take-up. Of the twenty-five Group 1 and Group 2 schools participating in cost-sharing, two-thirds received albendazole at a cost of 30 Kenyan shillings per family (US$0.40 in 2001), and one- third received both albendazole and praziquantel at a cost of 100 shillings

(approximately US$1.30). Whether praziquantel was given depended on the local prevalence of schistosomiasis. Since parents have 2.7 children in school on average, the average cost of deworming per child in cost-sharing schools was slightly more than US$0.30—still a heavily subsidized price, about one-fifth the cost of drug purchase and delivery through this program (at US$1.49) and 60 percent of the cost in the Tanzania program." **Kremer and Miguel 2007**, Pgs. 1015-1016.

74.

"Efforts to replace subsidies with sustainable worm control measures were ineffective: a drug cost-recovery program reduced take-up 80 percent; health education did not affect behavior, and a mobilization intervention failed." **Kremer and Miguel 2007**, Abstract, Pg. 1007.

75.

- "We estimate negative coefficients on the 2001 cost-sharing indicator variable when the dependent variable is hours worked, meals eaten, passing the primary school leaving exam, or log wage earnings (Tables S6-S9). The fact that coefficient estimates on the cost-sharing indicator are of opposite sign compared to the direct treatment effect, and typically smaller in absolute value, is reassuring." **Baird et al. 2016 - Appendix**, Pg. S11.
- "Because the temporary 2001 deworming treatment cost-sharing program substantially reduced take-up, it provides an additional, orthogonal source of variation in treatment, albeit with less statistical power. Reassuringly, the estimated effect of cost-sharing has the opposite sign of the main deworming treatment effect for 26 of the 30 outcomes presented in Tables I-IV (excluding the first outcome in Table 1, which was measured before cost-sharing was introduced), and this pattern seems extremely unlikely to occur by chance. In addition, stacking the data and using seemingly unrelated regression (SUR) estimation across outcomes, we reject the hypothesis that the cost-sharing coefficients are zero ($P<0.001$); see appendix section B for further details." **Baird et al. 2016**, Pgs. 28-29.
- For the statistical significance of these results under different specifications, see Tables S6-S9, Pgs. S24-S27, **Baird et al. 2016 - Appendix**.

76.

We have conducted an informal back-of-the-envelope calculation comparing the treatment effect sizes in **GiveWell, Deworming replicability adjustment, "Sensitivity analyses of the deworming effect" section**, which relies on preliminary results from the 15-year follow-up to **Miguel and Kremer 2004**. We may provide more formal analysis once these results have been made fully publicly available.

77.

See the "How well would the studies generalize to other settings?" section of our **2012 blog post** on the studies.

78.

- See our discussion of that study and how it relates to previous studies on the long-term effects of deworming **here**.
- "This paper analyzes the long run impact of a cluster-randomized trial in eastern Uganda that provided mass deworming treatment to a sample of preschool aged children from 2000 to 2003. An early impact evaluation of this intervention found that the treatment group, comprised of children aged 1-7, showed increased weight gain compared to controls (Alderman et al. 2007). Since there is now a large literature linking early life health, often proxied by weight, to long run outcomes (including cognitive, educational, health, and labor market outcomes), I use data collected in these communities 7-8 years after the end of the deworming trial to see whether children in treatment communities have higher scores than children in control communities on simple numeracy and literacy tests. I find that children who lived in treatment communities during the period in question have test scores 0.2-0.4 standard deviations higher than those in control parishes. Effects are larger for math than for English literacy scores. The effect is robust to a wide range of alternate specifications and inclusion of socioeconomic control variables, and to a placebo treatment test. Girls and children from the poorest income quintiles experience relatively larger gains." **Croke 2014**, Pg. 2

79.

"This study evaluates the economic consequences of the successful eradication of hookworm disease from the American South, which started circa 1910. The Rockefeller Sanitary Commission (RSC) surveyed infection rates and found that 40 percent of school-aged children in the South were infected with hookworm. The RSC then sponsored treatment and education

campaigns across the region. Follow-up studies indicate that this campaign substantially reduced hookworm disease almost immediately. Areas with higher levels of hookworm infection prior to the RSC experienced greater increases in school enrollment, attendance, and literacy after the intervention. No significant contemporaneous results are found for literacy or occupational shifts among adults, who had negligible prior infection rates. A long-term follow-up indicates a substantial gain in income that coincided with exposure to hookworm eradication. I also find evidence that the return to schooling increased with eradication." **Bleakley 2007**, abstract.

80.

Deworming substantially improved health and school participation among untreated children in both treatment schools and neighboring schools, and these externalities are large enough to justify fully subsidizing treatment." **Miguel and Kremer 2004**, abstract.

More at our **2012 blog post** and **full writeup** on the topic.

81.

Ozier 2011, Pg 9.

82.

"This paper explores positive and negative effects of the Integrated Neglected Tropical Disease (NTD) Control Initiative, consisting in mass preventive chemotherapy for five targeted NTDs, on Mali's health system where it was first implemented in 2007…Campaign processes and interactions with the health system were assessed through participant observation in two rural districts (8 health centres each)." **Cavalli et al 2010**, Pg. 1

83.

Praziquantel:

- "Praziquantel is administered orally at a standard dose of 40 mg/kg body weight. The most common adverse effects are gastrointestinal, including abdominal pain, nausea, vomiting and diarrhoea, and are usually mild and last less than 24 hours." **Danso-Appiah et al. 2008**. 2008, Pg 4.
- "Praziquantel and metrifonate were both found to be efficacious with few adverse events, although adverse outcomes were poorly assessed." **Danso-Appiah et al. 2008**, abstract.
- **Saconato and Atallah 2009**, Pg 20 lists clinical side effects from praziquantel based on the studies it reviews. Those whose 95% confidence intervals do not include zero are statistically significant effects: headache, nausea, abdominal pain, fever.
- **Notes from our site visit to the Schistosomiasis Control Initiative (SCI)** include reports of fainting and vomiting at a stakeholders' meeting. SCI's representative stated that these can be prevented by feeding children prior to treatment.

Albendazole:

- "Albendazole is administered orally (usually as single 400 mg dose), and reported adverse effects include gastrointestinal upsets, headaches, and dizziness, while rash, fever, elevated liver enzymes, and hair loss occur less frequently. There have been reports of elevated liver enzymes, headaches, loss of hair, low levels of white blood cells (neutropenia), fever, and itching if taken at higher doses and/or for a long period of time." **Danso-Appiah et al. 2008**, Pg 4.
- "Two trials looked at adverse events, but the trials were small. Further research is needed … Only two trials provided this information (Michaelsen 1985; Fox 2005). Fox 2005 found no serious adverse events (albendazole 0/46 versus placebo 0/43). Myalgia and cough were reported significantly more frequently in the placebo group compared to al- bendazole. Michaelsen 1985, which used tetrachlorethylene, re- ported that 17%(19/119: results not given for separate trial arms) of the children suffered adverse effects (nausea and ataxia) that began one and a half hours after treatment. All symptoms disappeared within four hours. This drug is not in current use as a deworming drug." **Taylor-Robinson, Jones, and Garner 2007**, abstract and Pg 21-22.

- "It has been suggested that resistance to deworming drugs may be a factor that limits the effectiveness of periodic deworming (**Hotez et al. 2006**). Some people have also questioned whether albendazole itself can adversely affect growth (Hotez et al. 2006)." **Taylor-Robinson, Jones, and Garner 2007**, Pg 27.

84.

Ibid.

85.

"A concern about the feasibility of sustainable control with BZAs is the possible emergence of drug resistance among human STHs. BZA resistance occurs because of the spread of point mutations in nematode-tubulin alleles. This phenomenon has already resulted in widespread BZA drug resistance among STHs of ruminant livestock. There is still no direct evidence for BZA resistance among human STHs, although such resistance could account for an observed failure of mebendazole for human hookworm in southern Mali, as well as a diminished efficacy against hookworm in Zanzibar following frequent and periodic use of mebendazole (Albonico and others 2003). PZQ resistance must also be considered, especially as it begins to be widely used in Sub-Saharan Africa (Hagan and others 2004). Should PZQ resistance develop, there will be new demands for antischistosomal drugs. Recently, the artemisins have shown activity against schistosomulae and were successful in protecting against S. japonicum in China (Hagan and others 2004)." Jamison et al. 2006, Pg 479.

86.

A 2011 review (which we have not deeply vetted) found no compelling evidence of resistance: "Geerts and Gryseels (2001) reviewed the reports on drug resistance in human helminths and concluded that two studies (De Clercq et al., 1997; Reynoldson et al., 1997) provided data suggestive for the development of AR in hookworms, but actually fell short of providing conclusive evidence. De Clercq et al. (1997) observed no reduction in the number of Necator eggs and a CR of only 22.9% after treatment with a single dose of MEB 500 mg. A standard egg hatch assay indicated that the Mali strain of N. americanus was almost twice as resistant to BZ as the laboratory reference strain (ED_{50} of 0.117 compared to 0.069). However, the significance of this differ- ence in ED_{50} is difficult to assess given the very different genetic backgrounds of the isolates. A similar study in the same region (Sacko et al., 1999) with a single dose of ALB 400 mg resulted in a CR of 51.4% and a ERR of 77.6%, both significantly higher than re- ported earlier by De Clercq et al. (1997). Thus the studies fell short of providing conclusive evidence of AR against BZ in Mali.

The most likely reason for the failure of PYR (10 mg/kg) in the treatment of Ancylostoma (ERR of 46% and CR of 13%) according to Reynoldson et al. (1997) was the development of resistance as a consequence of the drug's frequent use in the community over many years. However, the low number of patients (n = 15) and the high pre-treatment egg counts (mean baseline FEC = 869 EPG) may have affected the estimate of efficacy.

In Vietnam, a single dose MEB was found to have disappointing efficacy against hookworm infections (reduction of mean EPG rel- ative to placebo was only 31%) (Flohr et al., 2007). However, AR seemed unlikely as repeated dosing with MEB during 3 consecutive days in a second study resulted in a reduction of the mean EPG rel- ative to placebo by 63%. It should also be noted that the second study was conducted among adults (in contrast to children in the first study) with higher pre-treatment burdens compared to the first study (2210 EPG vs. 263 EPG), potentially confounding com- parison and/or leading to bias.

On Pemba Island, Zanzibar, the efficacy of MEB against hook- worms in school children appeared to have fallen over a period of 5 years, during which time the children were regularly treated with MEB (ERR fell from 82.4% to 52.1%). This suggested the possi- bility of emergence of MEB-resistant hookworms on Pemba Island (Albonico et al., 2003). In support, an in vitro study using an egg hatch assay showed a lower thiabendazole ED_{50}compared to the veterinary resistance-threshold for Haemonchus contortus. How- ever, this comparison between livestock and human worm species is far from ideal, and more studies are required before a specific efficacy/resistance threshold for human hookworms can be unequivocally agreed (Albonico et al., 2005) (see Section 7.2). Molecular studies were conducted on the hookworm population of Pemba Island but no evidence was found for the b-tubulin muta- tion at amino acid residue 200 (Phe/Tyr) (Albonico et al., 2004b; Schwenkenbecher et al., 2007).

No studies have been published on AR in A. lumbricoides. The presence of the Phe200Tyr SNP (single nucleotide polymorphism) in b-tubulin was detected in low frequency in T. trichiura from non-treated people from Kenya and at high

frequency in T. trichiura from treated people from Panama (Diawara et al., 2009). However, these SNP frequencies could not be linked to AR as sample sizes were small, anthelmintic efficacy was not assessed, and drug trea- ted and non-treated samples were from different locations.

To date all reports indicating disappointing efficacy among the BZs have concerned MEB, and even in studies where MEB had low efficacy (Sacko et al., 1999), ALB was used as the positive con- trol and showed extremely high efficacy against hookworms (See also Vercruysse et al., 2011). It is therefore of some concern that a recent report from Ghana has indicated a high failure rate for ALB in the treatment of hookworm infections (Humphries et al., 2011). Although the ERR was 82% following treatment of 102 in- fected subjects, the CR was only 61%. Even more worrying was the observation that within the group that did not respond to ALB treatment, FECs did not drop after treatment. While this study was not primarily designed as an anthelmintic trial, the work was thoroughly conducted and analyzed, and the ALB tablets were con- firmed as actually having been swallowed by all study subjects.

To conclude, the number of studies assessing AR in human STH is currently very limited, and the studies to date suffer from a num- ber of serious flaws: almost none deal with potential confounding factors (e.g. quality of the drugs), many are based on only low numbers of subjects and are significantly underpowered, the ab- sence of standardised protocols and diagnostic techniques, and a lack of any agreed thresholds for defining AR. Therefore, it remains uncertain still whether the reports on reduced efficacy in hook- worms represent genuine cases of AR, based on the selection of resistance alleles in the parasites, or rather, whether they simply reflect reduced efficacy." **Vercruysse et al. 2011**, pgs. 16-17.

87.

"Choking: The WHO has raised concerns about the prevalence of choking in young children (aged between 1 to 3 years), with sev- eral pages of recommendations about how to administer albenda- zole in tablet form without children choking (**http://www.who.int/** wormcontrol/newsletter/PPC8 eng.pdf) WHO 2007. Although common sense might suggest this is a rare occurrence, nevertheless some might argue there is a lack of evidence on the safety of administering deworming drugs to young children in tablet form in a community setting." Pg. 23.

88.

The Times of India 2012.

89.

- "In the past decade there have been an increasing number of studies on co-infections between worms and malaria. However, this increased interest has yielded results that have been at times conflicting and made it difficult to clearly grasp the outcome of this interaction. Despite the heterogeneity of study designs, reviewing the growing body of research may be synthesized into some broad trends: Ascaris emerges mostly as protective from malaria and its severe manifestations, whereas hookworm seems to increase malaria incidence. As efforts are made to de-worm populations in malaria endemic areas, there is still no clear picture of the impact these programmes have in terms of quantitative and qualitative changes in malaria." **Nacher 2011**, Abstract
- List of studies included with information on study design: **Nacher 2011, Additional file 1**

90.

- **Nacher 2011** reviews the evidence on the effect of deworming on malaria. It does not describe its inclusion criteria or give much detail on its search strategy: "Despite these difficulties, the present review aims to synthesize the growing number of studies that have explored the interactions between worms and malaria. Pubmed and google scholar searches were performed for malaria and any of the keywords worms, helminth, Ascaris, hookworm, Trichuris, or Strongyloides. This search identified published papers which were then studied for additional references." **Nacher 2011**, Pg. 1
- **Nacher 2011** identifies 4 studies as RCTs.
  - **Murray, Murray, Murray and Murray 1978**: "Comoro Islands [2]", **Nacher 2011, Additional file 1**, Pg. 1
  - **Brutus et al 2006**: "Madagascar [6]", **Nacher 2011, Additional file 1**, Pg. 4
  - **Brutus et al 2007**: "Madagascar [7]", **Nacher 2011, Additional file 1**, Pg. 4
  - **Kirwan et al 2010**: "Nigeria [24]", **Nacher 2011, Additional file 1**, Pg. 6

- One of the 4 studies (**Murray, Murray, Murray and Murray 1978**) does not appear to be a RCT: "For the present study, four groups of children with similar age and sex distribution were chosen from two closely neighboring hill villages. Group I consisted of 27 boys and 10 girls, ages 2 to 14, who had no recent history of malarial attacks, no splenomegaly and no malarial parasites visible in thick and thin smears of blood stained with Giemsa by the method of Shute and Maryon (5) but who had severe ascariasis...The children were then treated with the ascaricide anhydrous piperazine phosphate, 75 mg per kilogram daily for 2 days. Group II consisted of 26 boys and nine girls of ages 2 to 13 with similar findings who were treated with placebo tablets composed of aluminum hydroxide and magnesium trisilicate. Group III children were 17 boys and six girls ages 3 to 13 without parotid enlargement and forehead edema, without enlarged abdomens, without a history of visible worms in the stool and less than 5000 ova per gram of feces...They were treated with piperazine phosphate in the same dosage as group I. Group IV had 13 boys and four girls, ages 2 to 12, with findings similar to group III...They were treated with placebo tablets." **Murray, Murray, Murray and Murray 1978**, Pgs. 1363-1364
- **Salazar-Castanon, Legorreta-Herrera and Rodriguez-Sosa 2014** reviews the evidence on the effect of deworming on malaria. It does not appear to describe its inclusion criteria or its search strategy.
- It identifies one study as a RCT: **Abanyie et al 2013** (Table 3, **Salazar-Castanon, Legorreta-Herrera and Rodriguez-Sosa 2014**, Pg. 7), but **Abanyie et al 2013** appears to be a non-experimental re-analysis of **Kirwan et al 2010**.
  - "Methods: Data from a randomized controlled trial on the effect of antihelminthic treatment in Nigerian preschool-aged (6–59 months) children conducted in 2006–2007 were analysed to examine the effect of malaria and Ascaris co-infection on anaemia severity. Children were enrolled and tested for malaria, helminths and anaemia at baseline, four, and eight months. Six hundred and ninety subjects were analysed in this study. Generalized linear mixed models were used to assess the relationship between infection status and Ascaris and Plasmodium parasite intensity on severity of anaemia, defined as a haemoglobin less than 11 g/dL." **Abanyie et al 2013**, Abstract.
  - "The description of the study population, design, and methods of the original study are detailed in prior publications [19,20]." **Abanyie et al 2013**, Pg. 2
- We also searched Google scholar for studies that cite **Nacher 2011** and found **Wiria et al 2013** and **Kinung'hi et al 2015**.

91.

- "In the past decade, the topic was rediscovered, this time from an immunological angle. Depending on which publication one reads, it is not clear if the outcome of this interaction is beneficial [3], neutral [4] or harmful [5]. The studies on the interactions between worms and malaria in humans have been very different in design, in the age groups sampled, in the way the malaria outcome and the exposure to helminths were considered." **Nacher 2011**, Pg. 1
- "The default condition of the mammalian ancestral immune system was to be parasitized by gastrointestinal nematodes and other helminths, and acute responses to microparasites were tuned to this TH2/Treg skew. Researchers have long been unaware of the fact that worms significantly impact malaria, the strongest known selective force on the human genome. Despite a growing number of studies, and some emerging patterns, there is still scarce data on the immunological consequences of worms-malaria co-infections and the precise mechan- isms at play. Nevertheless, vaccine trials and vaccination campaigns in the tropics should definitely take worms into account [48].

> More research is needed to disentangle the underlying immunological mechanisms, the differences between different helminths, and the effect of age on the outcome of co-infections. The present review can cautiously conclude that worms, notably Ascaris, are associated with protection from severe complications and that they can, notably hookworm, lead to increased malaria incidence or prevalence. Thus, although it is tempting to rush to the conclusion that de-worming patients would reduce malaria, it still seems wise to be attentive to the potential scenario of an increase of severe malaria. Monitoring the incidence of malaria and severe malaria before and after vertical de-worming campaigns seems a minimum test to make sure there is a better understanding of what is going on at a population level, and that, for individual patients, it is best to follow the medical precept primum non nocere - first do no harm." **Nacher 2011**, Pgs. 3-4

92.

- "A controlled randomized trial of antihelminthic treatment was undertaken in 1996–1997 in a rural area of Madagascar where populations were simultaneously infected with Ascaris lumbricoides and Plasmodium falciparum. Levamisole was administered bimonthly to 164 subjects, randomized on a family basis, whereas 186 were controls. While levamisole proved to be highly effective in reducing Ascaris egg loads in the treated group (P < 10−3 at all bimonthly visits), subjects more than 5 years of age, treated with levamisole had a significant increase in their P. falciparum densities compared with controls (P = 0.02), whereas there was no effect of anti-helminthic treatment on children 6 months to 4 years of age. The demonstration of a clear negative interaction between Ascaris infection and malaria parasite density has important implications. Single community therapy programs to deliver treatments against several parasitic infections could avoid an increase of malaria attacks after mass treatment of ascariasis." **Brutus et al 2006**, Abstract
- "At each visit, finger prick thick and thin blood smears were made on all subjects. Smears were stained with Giemsa and 100 oil-immersion microscopic fields were examined for ma- laria parasites. Parasites and white blood cells were enumerated, and parasite density was calculated according to an assumed average of 8,000 leukocytes/mm3." **Brutus et al 2006**, Pg. 195
- "The main objective of this follow-up was to combine the observation of an entire malaria transmission season and the repeated treatment of intestinal helminths at intervals adapted to the life cycle of Ascaris (8 weeks from egg ingestion until sexual maturity of adult worms). At each visit, included subjects were clinically exam- ined and stool and blood samples were taken for malaria parasites and helminth search. Updating of questionnaires was also done on the same occasion. In addition, subjects belonging to the treated group were administered an anti- helminthic single-dose oral treatment of levamisole (3 mg/kg in children, 150 mg in adults) under control of the investiga- tors. At each visit, a multivitamin treatment (1/2 to 3 tablets every 2 months, each tablet containing 2500 IU vitamin A, 1.0 mg thiamine, 0.5 mg riboflavine, 7.5 mg nicotinamide, and 300 IU vitamin D3) was given to subjects from the control group." **Brutus et al 2006**, Pg. 195

93.

- "A controlled randomized trial of antihelminthic treatment was undertaken in 1996–1997 in a rural area of Madagascar where populations were simultaneously infected with Ascaris lumbricoides and Plasmodium falciparum. Levamisole was administered bimonthly to 164 subjects, randomized on a family basis, whereas 186 were controls. While levamisole proved to be highly effective in reducing Ascaris egg loads in the treated group (P < 10−3 at all bimonthly visits), subjects more than 5 years of age, treated with levamisole had a significant increase in their P. falciparum densities compared with controls (P = 0.02), whereas there was no effect of anti-helminthic treatment on children 6 months to 4 years of age. The demonstration of a clear negative interaction between Ascaris infection and malaria parasite density has important implications. Single community therapy programs to deliver treatments against several parasitic infections could avoid an increase of malaria attacks after mass treatment of ascariasis." **Brutus et al 2006**, Abstract
- "Relation between P. falciparum density (log-transformed) and treatment of A. lumbricoides in different age groups. Ambohimena, 1997", Table 2, **Brutus et al 2006**, Pg. 197

94.

"At each visit, depending on the month, 0–9 subjects (mean, 3.7) in the control group and 0–11 (mean, 4.2) in the levami- sole-treated group presenting with fever and parasitemia re- ceived oral chloroquine treatment. An overall proportion of 2.5% (control group) and 3.3% (treated group) received chlo- roquine. The maximum number of treated subjects was between February and June 1997, during the malaria transmission season." **Brutus et al 2006**, Pg. 196

95.

Table 1, **Brutus et al 2006**, Pg. 195

96.

- "A controlled randomized trial of anti-helminthic treatment was undertaken in 1996–1997 in a rural area of Madagascar where populations were simultaneously infected with Ascaris lumbricoides, Plasmodium falciparum, and Schistosoma mansoni. Levamisole was administered bimonthly to 107 subjects, whereas 105 were controls. Levamisole was highly effective in reducing Ascaris egg loads in the treated group (P < 10−3 at all visits), whereas it had no effect on schistosomiasis. Subjects 5–14 years of age, treated with levamisole, had a significant increase of their P. falciparum

densities compared with controls (P = 0.003). There was no effect of the treatment on children 6 months to 4 years of age, nor on adults > 15 years of age. This study confirms the results of a randomized trial, which showed a negative interaction in those > 5 years of age between Ascaris and malaria parasite density in another Malagasy population, submitted to a higher malaria transmission." **Brutus et al 2007**, Abstract

- "In the control group, at all visits except one (in the month of October 1996, one single suspected malaria attack), no subject showed an association of fever and parasitemia, with an indication for the administration of oral chloroquine. In the levamisole-treated group, there were four suspected clinical malaria occurrences (two in June 1996, one in February, and one in April 1997) who received chloroquine." **Brutus et al 2007**, Pg. 1092
- "The first trial was undertaken in a village on the western fringe of the central highlands of Madagascar where malaria is mesoendemic with a low transmission rate (three to nine infective bites per man per year),7 whereas this study was performed in a more elevated area, targeted by routine yearly DDT house-sprayings from 1993 to 1998. In this latter setting, malaria is hypoendemic and unstable, and transmission is much lower than in the former (less than one infective bite per man per year), with marked within- and between-year variations.9 As these differences in malaria transmission may explain, at least in part, that the concerned age groups are not exactly the same, it is, however, striking that in both studies, a negative Plasmodium–Ascaris interaction was significant in children 5–15 years of age. In addition, in this study, four clinical malaria accesses (association of fever and parasitemia) were suspected in the levamisole-treated group versus one only in the control group." **Brutus et al 2007**, Pg. 1093
- "At the same time, we performed a similar trial on a different population living at a higher altitude, also affected by malaria and ascaridiosis, but also situated in a Schistosoma mansoni transmission area." **Brutus et al 2007**, Pg. 1091

97.

- "For Necator americanus infection, only one subject was infected in the control group and none were infected in the treated group (data not shown)." **Brutus et al 2007**, Pg. 1092
- Table 1, **Brutus et al 2007**, Pg. 1092

98.

"Plasmodium prevalence and mean Plasmodium parasite density was significantly higher in the treatment group (44.9% and 2319 ± SE 511) compared to the placebo group (33.3% and 1471 ± 341) at baseline." **Kirwan et al 2010**, Abstract

99.

"Background: Helminth infections can alter susceptibility to malaria. Studies need to determine whether or not deworming programs can impact on Plasmodium infections in preschool children.
Methods: A double-blind placebo-controlled randomised trial was conducted to investigate the impact of anthelmintic treatment on Plasmodium infection in children aged 12-59 months. Children were randomly assigned to receive either albendazole or placebo every four months for 12 months with a follow-up at 14 months.
Results: 320 children (out of 1228, 26.1%) complied with all the follow-up assessments. Plasmodium prevalence and mean Plasmodium parasite density was significantly higher in the treatment group (44.9% and 2319 ± SE 511) compared to the placebo group (33.3% and 1471 ± 341) at baseline. The odds of having Plasmodium infection increased over time for children in both the placebo and treatment groups, however this increase was significantly slower for children in the treatment group (P = 0.002). By month 14, mean Plasmodium density had increased by 156% in the placebo group and 98% in the treatment group but the rate of change in Plasmodium density was not significantly different between the groups. The change from baseline in haemoglobin had a steeper increase among children in the treatment group when compared to the placebo group but this was not statistically significant.
Conclusions: Repeated four-monthly anthelminthic treatments for 14 months resulted in a significantly lower increase in the prevalence of Plasmodium infection in preschool children which coincided with a reduction in both the prevalence and intensity of A. lumbricoides infections." **Kirwan et al 2010**, Abstract

100.

Table 1, **Kirwan et al 2010**, Pg. 4

101.

- "Background: Helminth infections are proposed to have immunomodulatory activities affecting health outcomes either detrimentally or beneficially. We evaluated the effects of albendazole treatment, every three months for 21 months, on STH, malarial parasitemia and allergy.
  Methods and Findings: A household-based cluster-randomized, double-blind, placebo-controlled trial was conducted in an area in Indonesia endemic for STH. Using computer-aided block randomization, 481 households (2022 subjects) and 473 households (1982 subjects) were assigned to receive placebo and albendazole, respectively, every three months. The treatment code was concealed from trial investigators and participants. Malarial parasitemia and malaria-like symptoms were assessed in participants older than four years of age while skin prick test (SPT) to allergens as well as reported symptoms of allergy in children aged 5–15 years. The general impact of treatment on STH prevalence and body mass index (BMI) was evaluated. Primary outcomes were prevalence of malarial parasitemia and SPT to any allergen. Analysis was by intention to treat. At 9 and 21 months post-treatment 80.8% and 80.1% of the study subjects were retained, respectively. The intensive treatment regiment resulted in a reduction in the prevalence of STH by 48% in albendazole and 9% in placebo group. Albendazole treatment led to a transient increase in malarial parasitemia at 6 months post treatment (OR 4.16(1.35–12.80)) and no statistically significant increase in SPT reactivity (OR 1.18(0.74–1.86) at 9 months or 1.37 (0.93–2.01) 21 months). No effect of anthelminthic treatment was found on BMI, reported malaria-like- and allergy symptoms. No adverse effects were reported.
  Conclusions: The study indicates that intensive community treatment of 3 monthly albendazole administration for 21 months over two years leads to a reduction in STH. This degree of reduction appears safe without any increased risk of malaria or allergies." **Wiria et al 2013**, Abstract
- Table 3, "Effect of three-monthly albendazole treatment on malaria outcomes: Malarial parasitemia by microscopy", **Wiria et al 2013**, Pg. 6
- Table 4, "Effect of three-monthly albendazole treatment on malaria outcomes: Malarial parasitemia by PCR", **Wiria et al 2013**, Pg. 6

102.

- "There was no difference in the incidence of fever and additional malaria-like symptoms between the two treatment arms (table S2 in Appendix S1 p10)." **Wiria et al 2013**, Pg. 6
- "The p-values are generated from Cox regression of albendazole treatment over time with robust SEs to allow for within-subject and within household clustering and no significant effects were found (P>0.05)." **Wiria et al 2013, Appendix S1**, Pg. 10

103.

Table 1, **Wiria et al 2013**, Pg. 3

104.

- "Background: Some studies have suggested that helminth infections increase the risk of malaria infection and are associated with increased number of malaria attacks and anaemia. Thus interventions to control helminth infections may have an impact on incidence of clinical malaria and anaemia. The current study assessed the impact of two anthelmintic treatment approaches on malaria infection and on anaemia in school and pre-school children in Magu district, Tanzania.
  Methods: A total of 765 children were enrolled into a prospective randomized anthelmintic intervention trial following a baseline study of 1546 children. Enrolled children were randomized to receive either repeated treatment with praziquantel and albendazole four times a year (intervention group, 394 children) or single dose treatment with praziquantel and albendazole once a year (control group, 371 children). Follow up examinations were conducted at 12 and 24 months after baseline to assess the impact of the intervention. Stool and urine samples were collected and examined for schistosome and soil transmitted helminth infections. Blood samples were also collected and examined for malaria parasites and haemoglobin concentrations. Monitoring of clinical malaria attacks was performed at each school during the two years of the intervention.
  Results: Out of 1546 children screened for P. falciparum, S. mansoni, S. haematobium, hookworm and T. Trichiura at baseline, 1079 (69.8%) were infected with at least one of the four parasites. There was no significant difference in malaria

infection (prevalence, parasite density and frequency of malaria attacks) and in the prevalence of anaemia between the repeated and single dose anthelmintic treatment groups at 12 and 24 months follow up (p > 0.05). However, overall, there was significant improvement in mean haemoglobin concentrations (p Conclusions: These results suggest that repeated anthelmintic treatment did not have an impact on malaria infection compared to single dose treatment. However, both treatment approaches had overall impact in terms of improvements of haemoglobin levels and hence reductions in prevalence of anaemia." **Kinung'hi et al 2015**, Abstract

- "From each school, school chil- dren aged 6–13 years (grades I-V) were randomly selected and included in the study. The aim was to get at least 100 children per school. Where the required number of 100 school children was not reached, pre-school children aged 3–5 years were also enrolled into the study. Selection of pre-school children was made conveniently whereby par- ents and guardians living in the community surrounding each school were requested to bring their children to the examination centre." **Kinung'hi et al 2015**, Pg. 2

105. Table 1, **Kinung'hi et al 2015**, Pg. 5

106. **World Health Organization. Preventive chemotherapy in human helminthiasis**, Pg 41.

107. **World Health Organization. Preventive chemotherapy in human helminthiasis**, Pg 41.

108. **World Health Organization. Preventive chemotherapy in human helminthiasis**, Pg 41.

109. "The age-dependent patterns of infection prevalence are generally similar among the major helminth species, exhibiting a rise in childhood to a relatively stable asymptote in adulthood (figure 24.1). Maximum prevalence of A. lumbricoides and T. trichiura is usually attained before five years of age, and the maximum prevalence of hookworm and schistosome infec- tions is usually attained in adolescence or in early adulthood. The nonlinear relationship between prevalence and intensity has the consequence that the observed age-prevalence profiles provide little indication of the underlying profiles of age inten- sity (age in relation to worm burden). Because intensity is linked to morbidity, the age-intensity profiles provide a clearer understanding of which populations are vulnerable to the different helminths (figure 24.1). For A. lumbricoides and T. trichiura infections, the age-intensity profiles are typically convex in form, with the highest intensities in children 5 to 15 years of age [**Bundy et al. 2004**]. For schistosomiasis, a convex pattern is also observed, with a similar peak but with a plateau in adolescents and young adults 15 to 29 years of age (Kabatereine and others 1999). In contrast, the age-intensity profile for hookworm exhibits considerable variation, although intensity typically increases with age until adulthood and then plateaus (Brooker, Bethony, and Hotez 2004). In East Asia it is also common to find the highest intensities among the elderly. However, more generally, children and young adults are at higher risk of both harboring higher levels of infection (thus greater levels of morbidity) and becoming reinfected more quickly. Both may occur at vital stages in a child's intellectual and physical development." **Hotez et al. 2006**, Pgs 469-470.

110. "The aim is morbidity control: periodic treatment of at-risk populations will cure subtle morbidity and prevent infected individuals from developing severe, late-stage morbidity due to schistosomiasis." **World Health Organization. Preventive chemotherapy in human helminthiasis**, Pg 60.

111. "Single-dose oral therapies can kill the worms, reducing ... infections by 99 percent ... Reinfection is rapid, however, with worm burden often returning to eighty percent or more of its original level within a year ... and hence geohelminth drugs must be taken every six months and schistosomiasis drugs must be taken annually." **Miguel and Kremer 2004**, Pg 161.

112.

- We found that the claims made in the block quote in the section on "Externalities for the untreated" in the intervention report did not substantially change from **Ozier 2011** to **Ozier 2015**.
- We checked that the claims made in the paragraph starting with “The study's headline effect is that as adults” and ending with “positive effects on school performance (though not on IQ)” in the section of the intervention report on “Developmental impacts” had not substantially changed between **Baird et al. 2012** and **Baird et al 2015 - November**. We also checked if the estimates from **Baird et al. 2012** that we use for our cost-effectiveness analysis (CEA) for deworming (see **above section**) had changed (“Treatment effect of deworming on Ln(Total labor earnings), monthly,” “Proportion of dewormed children that end up working for wages,” and “Years of treatment assigned in the Miguel and Kremer 2004 study”). We found that **Baird et al 2015 - November** reached substantially the same conclusions as **Baird et al. 2012**. The estimates of the effect of deworming on labor earnings and hours worked increased slightly and we have updated our CEA accordingly. **Baird et al 2015 - November** and **Baird et al. 2015 - Appendix** do not seem to report the effect of deworming on health expenditures or English vocabulary tests, so we could not check its conclusions for those outcomes. The authors’ estimate of the internal rate of return (IRR) also appears to have increased from 24.7% to 32.2%. We have not checked whether the definition of the IRR or the inputs to the IRR changed between papers. The authors’ estimate of the IRR does not play an important role in our view of the cost-effectiveness of deworming; we have conducted our own cost-effectiveness estimate using what we see as the key outcomes from this study, among other inputs (see **above**). Details on our comparison of **Baird et al. 2012** and **Baird et al 2015 - November** are below:
    - **Log of total labor earnings in the past month among wage earners.** The estimate of the effect of deworming on the log of total labor earnings in the past month among wage earners changed slightly. **Baird et al. 2012** estimates an increase in the log of total labor earnings in the past month among wage earners of 0.253 (SE: 0.093) (Table 6, Pg. 53). **Baird et al 2015 - November** estimates an increase in the log of total labor earnings in the past month among wage earners of 0.269 (SE: 0.085) (Table 4, Pg. 44).
    - **Proportion working for wages.** The proportion of the control group working for wages, on which we base our estimate of “Proportion of dewormed children that end up working for wages” (because the proportion of the treatment group found working for wages is not significantly different), does not appear to have changed. **Baird et al. 2012** reports that the control group has a mean of “In Wage Employment” of 0.166 (Supplementary Appendix Table A2, Pg. iv). It also reports that the control group has 710 observations of the log of total labor earnings in the past month (Table 6, Pg. 53) and the control group has 5,084 observations of “Hours worked across all sectors in last week” in the “Full sample” (Table 3, Pg. 50). It is our understanding that an observation is only recorded for the log of total labor earnings in the past month if the person was working for wages. **Baird et al 2015 - November** does not report the mean of “In Wage Employment” in the control group. However, it also reports that the control group has 710 observations of the log of total labor earnings in the past month (Table 4, Pg. 44) and the control group has 5,084 observations of “Hours worked across all sectors in last week, full sample” (Table 3, Pg. 43). We do not know what explains the difference between ~14% (710/5084) and the 16.6% reported for the mean of “ln Wage Employment” (and **Baird et al 2015 - November** does not seem to provide an explanation) but the difference is small and we would guess that it results from small adjustments to the data to account for things like missing information.
    - **Hours worked.** The estimates of the effect of deworming on hours worked changed slightly from 3.40 (SE: 1.39) to 3.49 (SE: 1.42) hours for men and from 0.29 (SE: 1.34) to 0.32 (SE: 1.36) for women. **Baird et al. 2012** finds: “We first estimate deworming impacts on total hours worked in the last week. Among all KLPS respondents, deworming increased mean hours worked by 1.53 hours (s.e. 1.03 hours, Table 3, Panel A) on a control group mean of 18.4 hours. While this mean impact is not statistically significant at traditional confidence levels, a Kolmogorov-Smirnov test rejects equality of the hours worked distribution between the treatment and control groups at 90% confidence (p- value=0.09). Here and below we estimate impacts separately for males and females given the different marital and fertility patterns, family constraints, labor market opportunities and leisure options available by gender in Kenya. The hours worked effects are much larger among males, with an increase of 3.40 hours (s.e. 1.39) on a control group mean for males of 20.3 hours, a 16.7% increase significant at 95% confidence. Effects for all females are small and not statistically

significant, at 0.29 hours (s.e. 1.34)" (Pg. 24). **Baird et al 2015 - November** finds "Average weekly hours worked in the control group are quite low, at 20.3 for men and 16.3 for women (although many women in our sample are engaged in home production or child-rearing activities, and time spent on these activities was not systematically collected in KLPS-2). Among men, deworming increased time spent working by 17%, or 3.49 hours per week (SE 1.42, P < 0.05, Table 3, Panel A). In contrast, estimated effects on non-household work hours among women are small [0.32 (SE: 1.36), Pg. 43]. It is worth noting that three quarters of both the treatment and control groups are no longer in school by the time of the survey (Table 2). In this subpopulation, treated women worked 2.14 more hours per week, and although we cannot reject the hypothesis of no effect for women, we also cannot reject the hypothesis of equal treatment effects by gender" (Pg. 21).

- **Large shift into the manufacturing sector. Baird et al 2015 - November** reaches substantially the same conclusions as **Baird et al. 2012**. **Baird et al. 2012** finds that "Deworming treatment leads to pronounced shifts in the occupation of employment, out of relatively low-skilled and low-wage sectors into better paid and higher work intensity sectors (Table 6, Panel A). Deworming treatment respondents are three times more likely to work in manufacturing from a low base in the full sample of 0.005 (coefficient 0.010, s.e. 0.004)." (Pg. 34). **Baird et al 2015 - November** finds "Deworming treatment also leads to shifts in occupational choice (Table 3, Panel C). Treatment respondents are three times more likely to work in manufacturing (coefficient 0.0110, P < 0.05) from a low base of 0.005" (Pg. 22).
- **Meals consumed and overall consumption. Baird et al 2015 - November** reaches substantially the same conclusions as **Baird et al. 2012**. **Baird et al. 2012** finds: "We do not have complete data from a consumption module15, but did collect data on the number of meals respondents consumed, and find large deworming impacts. Deworming treatment respondents miss 0.096 fewer meals per day (s.e. 0.028, 99% confidence, Table 3, Panel B) than the control group, and the externality impact is also large and positive (0.080, s.e. 0.023, 99% confidence)" (Pg. 26). Footnote 15 in **Baird et al. 2012** states: "A consumption expenditure module was collected as a pilot for roughly 5% of the KLPS-2 sample during 2007- 2009, for a total of 255 complete surveys. The estimated treatment effect for total per capita consumption is near zero and not statistically significant (-$13, s.e. $66, trimming the top 2%), but the confidence interval is large and includes substantial gains, since average per consumption consumption is $584" (Pg. 26). **Baird et al 2015 - November** finds: "Living standards can be assessed using data on either consumption or earnings. We do not have data on overall consumption, but do have data on the number of meals consumed. Treatment respondents eat 0.095 more meals per day (SE 0.029, P < 0.01, Table 4, Panel A). The increase in meals eaten is larger for men, at 0.125 meals/day (P < 0.01) than for women (0.051 meals), implying that treatment males miss just under one fewer meal each week than control males" (Pg. 23). **Baird et al. 2015 - Appendix** states: "A consumption expenditure module was collected as a small pilot for 255 respondents. The estimated effect on total per capita consumption is near zero and not statistically significant but the confidence interval is large and includes both substantial gains and losses (not shown)" (Pg. S11).
- **Self-reported health. Baird et al 2015 - November** reaches substantially the same conclusions as **Baird et al. 2012**. **Baird et al. 2012** finds "Respondent reports that their health was "very good" rose by 4.1 percentage points (s.e. 1.8, significant at 95% confidence, Table 2, Panel A), on a base of 67.3% in the control group" (Pg. 21). **Baird et al 2015 - November** finds "Respondent reports that their health was "very good" rose by 4.0 percentage points (SE 1.8, P < 0.05), on a base of 67.3% in the control group" (Pg. 19).
- **Physical growth and health expenditure. Baird et al 2015 - November** appears to reach substantially the same conclusions on physical growth as **Baird et al. 2012**. **Baird et al 2015 - November** and **Baird et al. 2015 - Appendix** did not report on health expenditures. We state in the section on "Developmental impacts" that **Baird et al. 2011** "found a positive impact on meals consumed though not on overall consumption and gains on self-reported health though not on height or weight-for-height (and the treatment group had higher health expenditures)" and that "**Baird et al. 2012**, the updated version of **Baird et al. 2011**, reaches substantially the same conclusions." **Baird et al 2015 - November** states "Although we find no long-term effects on physical growth or body mass index, there is some evidence of persistent health gains in terms of self-reported health and reduced miscarriage" (Pg. 19). **Baird et al 2015**

- November and **Baird et al. 2015 - Appendix** did not report on health expenditure (we searched for "expenditure" and "spending" in both).

- **Test scores.** **Baird et al 2015 - November** reaches substantially the same conclusions as **Baird et al. 2012** on the effect of deworming on the passing rate for the secondary school entrance exam. **Baird et al 2015 - November** and **Baird et al. 2015 - Appendix** does not seem to have reported on the English vocabulary tests. **Baird et al. 2012** states: "There is suggestive evidence that deworming improved human capital: English vocabulary knowledge (collected in 2007-09) is slightly higher in the treatment group (0.076 standard deviations in a normalized distribution, s.e., 0.055), and the passing rate improved on the key primary school graduation exam, the Kenya Certificate of Primary Education (4.8 percentage points on a base of 50.5%, s.e. 3.1, Table 2, Panel B), although neither is significant. If we focus on the subsample of respondents who are no longer in school – a natural subsample of interest in the analysis of labor market impacts to follow – we find larger test score impacts. Note that there is no statistically significant difference in the proportion of treatment and control group students who are currently out-of-school at the time of the follow-up survey (both are at 75%), nor are there any significant differences across these groups along observable dimensions (appendix Table A1) nor is there differential selection into the out-of-school subsample along a observable characteristics across the treatment and control groups (appendix Table A2), including by gender, making this a reasonable comparison. The average gain on English vocabulary in the out-of-school subsample is 0.107 s.d. units (s.e. 0.052, significant at 95%), with large associated externality gains of 0.149 per 1,000 additional treatment pupils within 6 km (s.e. 0.047, significant at 99%). There is also an increase of 6.1 percentage points in the KCPE passing rate (on a base of 41.3%), and once again significant externalities (8.3 percentage points, significant at 99%). There is no clear gender pattern, with males showing somewhat larger gains in English vocabulary and females on passing the primary school graduation exam." (Pg. 23). **Baird et al. 2015 - Appendix** finds an increase of 0.050 (SE: 0.031) in the "Passed secondary school entrance exam during 1998-2007 indicator" (Pg. S37). **Baird et al 2015 - November** and **Baird et al. 2015 - Appendix** does not seem to have reported on the English vocabulary tests.
- **Cognition.** **Baird et al 2015 - November** reaches substantially the same conclusions as **Baird et al. 2012**. We state in the section on "Developmental impacts" that **Baird et al. 2011** found that "While the participants were still in school, the treatment had small, non-statistically significant positive effects on school performance (though not on IQ)" and that "**Baird et al. 2012**, the updated version of **Baird et al. 2011**, reaches substantially the same conclusions." **Baird et al 2015 - November** states: "Our evidence suggests that health interventions among school-aged children, which are too late in life to affect cognition or height, can have long-run impacts on labor outcomes by affecting the amount of time people spend in school or work" (Pg. 36).
- **Internal rate of return.** The authors' estimate of the internal rate of return (IRR) appears to have changed. We have not checked that the papers have the same definition of the IRR or if the inputs to the IRR changed. **Baird et al. 2012** states: "The IRR in the case of no health spillovers is 24.7% per annum for full subsidies, and with health spillovers it rises to 42.0% (Table 4, Panel D)" (Pg. 31). **Baird et al 2015 - November** states: "The annualized social IRR with no health spillovers ([L_2,y] = 0) is very high at 32.2%, and with health spillovers is a massive 51.6%" (Pg. 33).

113. **Giving What We Can, An update on the effectiveness of Deworm the World Initiative (DtWI), 2015**