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Mass Deworming Intervention Report - Supplementary Analysis

Contents

Introduction

In addition to some key considerations described in our main write-up about mass deworming here, this document provides some supplementary analysis to help model the cost-effectiveness of mass deworming:

a) We review evidence on the **health effects** of worm infections in the presence of **comorbidities**, i.e. how worm infections affect the health of someone with other morbidities such as malaria.

b) We model the impact of the potential development of **drug resistant** worms, i.e. worms that no longer respond to drug treatment.

c) SoGive believes that we should have a **sceptical prior opinion** about whether mass deworming leads to improvements in long-run economic productivity.

Key conclusions from this document and how they relate to SoGive's full analysis can be found here.

Supplementary Analysis

a) Health Effects in the Presence of Comorbidities

Background:

The evidence on mass deworming shows fairly small short-run effects on health. Nevertheless, since deworming is a medical intervention, SoGive believes it is important to carefully review the health effects of deworming. We have reviewed several studies analysing the impact of worm

infections on comorbidities. These studies are mostly not randomised controlled trials (RCTs), which are the gold standard for establishing causality in effectiveness research, but are animal experiments or retrospective data analyses. We have not thoroughly attempted to verify which studies demonstrate the most plausible strategies for establishing causality, and so more work is needed on this analysis. However, the conclusions from these studies provide some indicative evidence on the effects of mass deworming on comorbidities. As described below, and as summarised in our literature review, the studies suggest that there might be cases where deworming exacerbates the harms of comorbidities, though these are likely offset by cases where deworming mitigates such harms.

Malaria:

The effects of deworming on malaria are highly uncertain. GiveWell's analysis of a combination of RCTs and observational studies suggests that deworming may increase the presence of malaria parasites in the blood and/or the density of malaria parasites in the blood in school-aged children. However, the studies investigated by GiveWell do not show evidence that deworming causes more severe malaria or increased incidence of symptomatic malaria cases. Nacher 2011 concludes that one helminth, Ascaris, may protect against malaria, while another, Hookworm, may have the opposite effect.

HIV

We conclude that deworming for schistosomiasis probably has a favourable effect on reducing HIV virus acquisition, although our confidence in the evidence is low. One published systematic review, Salgame et al. 2013, finds that worm infections may compromise immune responses to HIV, although adverse effects of anthelmintic treatment cannot be ruled out, and the quality of studies is weak. Urogenital schistosomiasis is likely to increase susceptibility to HIV infection.[1] The authors hypothesise that malnutrition caused by worm infections may increase susceptibility to HIV infection. A second published systematic review, Furch et al. 2020, also concludes that urogenital schistosomiasis increases the risk of HIV acquisition. However, their findings also raise the possibility that worm parasites could activate the immune system and help protect against death and HIV disease progression, though evidence on this is inconsistent. To the best of our knowledge, none of the studies found in these systematic reviews are human experimental studies, which are unlikely to be feasible, since they would require randomisation of deworming treatment across a large sample of HIV-infected individuals. Non-experimental studies may be subject to several issues, such as publication bias and failure to meet econometric assumptions.

We also identified some additional studies not contained in these published systematic reviews, which we summarise in our own literature review. These studies largely support the hypothesis

[1] Urogenital schistosomiasis is caused by the parasite *Schistosoma haematobium*, which is targeted by GiveWell-recommended charities in some of their programmes. *Schistosoma haematobium* is fairly prevalent in areas where GiveWell-recommended charities currently operate. Prevalence of moderate-to-heavy infections for *Schistosoma haematobium* is around 3.7%, compared to 4.8% in total among other worm infections.

that worm infections increase the risk of HIV acquisition. One animal experiment (Chenine et al. 2008) finds that "acute schistosomiasis significantly increases the risk of de novo AIDS virus acquisition", while another (de Bruyn 2011) finds that deworming improved the immune response to HIV vaccine. However, the additional non-experimental human studies we identified produce conflicting results, since some of these studies find that worm infections improve or have no impact on HIV outcomes. Overall, our impression is that the evidence tentatively suggests deworming is likely to reduce HIV virus acquisition, and may therefore have positive flow-on effects in areas where HIV is widespread.

Other Comorbidities:

We identified five systematic reviews which analyse the effects of worm infections on other comorbidities (besides malaria and HIV). Van Riet et al. 2007 finds that worm infections may help prevent allergies and possibly other inflammatory diseases. However, worm-infected individuals may respond less strongly to antigens like vaccines. Maizels and McSorley 2016 similarly concludes that worm infections may benefit the host by lessening "allergic, autoimmune, and inflammatory reactions", but may cause harm by "reducing vaccine responses, increasing susceptibility to coinfection and potentially reducing tumor immunosurveillance". Salgame et al. 2013 notes that worm infection may increase the risk of progression from latent to active tuberculosis. Berbudi et al. 2015 concludes that worm infection is likely to delay the onset of type 1 diabetes and may also reduce the onset of type 2 diabetes, while Rennie et al. 2021 finds that infection was associated with improved metabolic function.

We also identified some additional studies not contained in these published systematic reviews, as summarised in our own literature review. Fenton 2013, using a theoretical mathematical model, states that "the benefits of deworming, although clear for reducing the morbidity due to helminth infection per se, are unclear regarding the outcome of coinfections and comorbidities." Fenton also argues that the interactions between worm parasites and other pathogens may depend on the magnitude of the worm burden. Specifically, Fenton hypothesises that light worm burdens could potentially improve life expectancy, but that increasing worm burdens beyond a certain threshold is likely to worsen life expectancy (see Figure 3). SoGive's main analysis of deworming (see "Health Effects in the Presence of Comorbidities") provides more details on the limitations and implications of this study, but we ultimately conclude that it is difficult to draw concrete empirical conclusions from Fenton's mathematical model.

The remaining six studies in our literature review suggest that worm infections may have positive effects on a host with comorbidities, such as asthma (Elliott et al. 2011, which is a RCT) and ranavirus (Wuerthner et al. 2017). However, evaluating these individual studies alongside the systematic reviews, to which we allocate more weight, we conclude that on balance the effects of deworming on comorbidities are highly uncertain. On one hand, worm infections appear to be protective against inflammatory diseases. On the other hand, worm infections may reduce the efficacy of vaccines and increase the risk of progression from latent to active tuberculosis.

Cost-Effectiveness Adjustment:

In our mass deworming cost-effectiveness model, we include a small and subjective 3% positive adjustment to account for the potential benefits of deworming due to reductions in HIV acquisition. This adjustment is small, because the evidence described above does not consistently point to favourable effects on HIV outcomes.

Although the evidence on inflammatory diseases and malaria seems to indicate a greater likelihood of negative effects, we do not include any negative adjustment for two reasons. Firstly, these effects may be offset by the positive impact of deworming on vaccine efficacy and tuberculosis. Secondly, if the effects of deworming on malaria were severe, these would likely be partially accounted for in the results from mass deworming RCTs, through measured effects on child weight and height gain, haemoglobin levels, and mortality. This is because the most severe effects caused by malaria, such as mortality, are primarily borne by children, and this is also the age group who participates in mass deworming RCTs. The most recent meta-analysis on mass deworming, a 2019 Cochrane review, reports a small and non-significant reduction in mortality as a result of multiple dose mass deworming, among studies of children aged 1-6. This suggests that mass deworming is not likely to have increased malaria mortality during these RCTs. Therefore, we do not adjust the cost-effectiveness of mass deworming due to effects on malaria or other comorbidities besides HIV.

b) Drug Resistance

Modelling the Probability of Drug Resistance:

In our main analysis of deworming, we note that anthelmintic drug resistance is widespread in *livestock* soil-transmitted helminths (STH), but there is no conclusive evidence that anthelmintic resistance has occurred in *human* STH.

Our drug resistance model aims to estimate the probability that mass deworming in 2022 (around 17 years after mass deworming first began on a large scale) causes drug resistance to develop in humans (either this year or in the future), holding constant all past and future deworming.[2] This model allows us to isolate the benefits and harms of undertaking mass deworming in any given year. The model relies on estimating a prior expectation about the probability that mass deworming in humans causes drug resistance. This prior expectation answers the question: If it were the start of year 1 of mass deworming, what is the probability that mass deworming of humans, as currently carried out, will ever cause drug resistance?

The development of drug resistance is often gradual and does not reduce efficacy to zero (see p. 419-420). Anthelmintic resistance is considered (p.38) to be present when treatment reduces worm burdens by less than 95%, and when the 95% confidence interval includes a worm

[2] For example, holding constant mass deworming between 2023 and 2028, the additional year of mass anthelmintic-drug consumption in 2022 could lead to the development of drug resistance in 2029. Our model would likely overestimate the harms of drug resistance if drug resistance occurs too far into the future, because of future reductions in worm burdens caused by better hygiene and poverty alleviation.

burden reduction of less than 90%. Our interpretation is that a 10% reduction in treatment efficacy would be evidence of drug resistance. In our simple model, we therefore try to estimate our prior probability that mass deworming causes a 10% reduction in treatment efficacy due to drug resistance.

At the start of year 1 of mass deworming, how likely would it be that mass deworming leads to drug resistance (a 10% reduction in treatment efficacy)? Drug resistance in livestock STH is commonplace (footnote 85), but deworming is typically more frequent for livestock (often reaching five times (p.17) per year compared to once or twice for humans). Furthermore, lower treatment coverage in humans may help delay and slow down resistance (see "Drug Resistance" here for details). Given the widespread drug resistance in livestock STH and the potential mitigating factors for human deworming, we estimate a prior probability of around 50% that drug resistance (a 10% reduction in treatment efficacy) would occur in human STH.

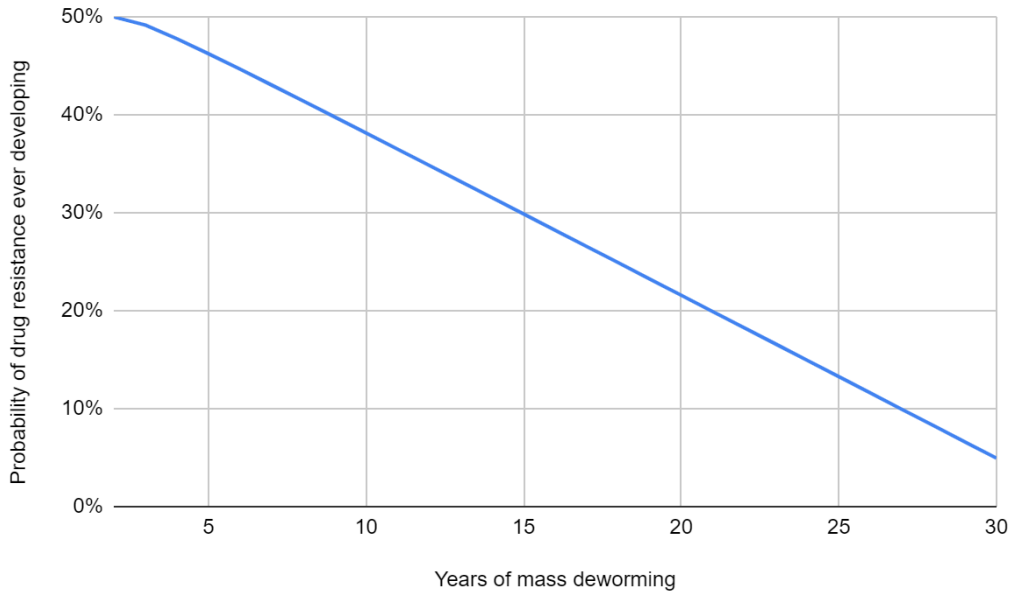
We still need to estimate the probability as of year 17 that drug resistance will develop, after 16 years of no resistance in human STH. In part 1 of our simple model, for each of the prior 16 years, we update our expectation downwards, since this is some evidence against the hypothesis that mass deworming in humans causes drug resistance. We allocate a probability of 0% for every year that drug resistance did not occur prior to 2022, while we allocate our prior probability (50%) for the start of year 1. We then take a weighted average of these probabilities to estimate an updated probability at the start of year 17. For a prior probability of 50%, the probability at the start of year 17 is 2.9%. This part of the model implies that the probability of drug resistance approaches zero as the number of years of mass deworming approaches infinity. In other words, we assume that a large number of years without seeing drug resistance is evidence that drug resistance will not occur.

In part 2 of our model, we account for the added risk of drug resistance as the volume of consumed anthelmintic drugs increases. Austin et al. (1999) note that "there is a critical level of drug consumption required to trigger the emergence of resistance to significant levels" (p.1156). This implies a counteracting effect on part 1 of the model, as the probability of reaching that critical level increases after more years of mass deworming. In part 2 of our model, we estimate how far we are along the trajectory of drug consumption, relative to the maximum number of years after which drug resistance is likely to develop. Austin et al. (1999) report that there can be long periods of no resistance before a rapid increase in resistance frequency. For example, resistant *Staphylococcus aureus* emerged after 30 years of vancomycin use in hospital settings in Japan and the USA (p.1152). Therefore, we roughly approximate that we are 17 / 30 = 57% of the way towards the maximum length of time required to reach the critical level where drug resistance develops.

To combine parts 1 and 2 of our model, for any given year, we take a weighted average of a) the probability from part 1 and b) our prior probability. These two factors are weighted by how far we are along the trajectory of drug consumption. If we are further along the trajectory, our prior probability is less credible, and the more we want to downgrade the probability of drug resistance. Given our prior of 50% that drug resistance would ever develop, in year 17 our updated probability is 2.9% * 57% + 50% * (100% - 57%) = 24.9%. Figure 1 illustrates the

decreasing probability as the number of years of mass deworming increases. The early years of mass deworming provide little evidence to update our beliefs about the probability of drug resistance ever developing, but we update our expectation downwards as we approach 30 years of mass deworming.

Figure 1



Future research could focus on estimating the volume of drug consumption (i.e. number of drugs) historically required to lead to resistance against other drugs.

Cost-Effectiveness Adjustment:

To assess the impact of potential drug resistance on the cost-effectiveness of mass deworming, consider a world where mass deworming charities have a binary choice between mass deworming and no deworming. Our key concern is how drug resistance might affect children with moderate-to-heavy worm burdens, who are generally symptomatic, and may otherwise obtain deworming tablets through *unprogrammed* deworming (such as from a chemist or healthcare centre) even in the absence of mass deworming programmes. On the other hand, mass deworming provides access to treatment for many children with moderate-to-heavy worm burdens who would otherwise not have access to deworming tablets. For this model, we assume that light worm burdens have no effect on children (see section “Lighter Worm Burdens” here for details on the effects of different worm intensities).[3]

The question is therefore, for each individual mass deworming treatment, how much more likely is it that a given treatment protects a child who would otherwise be untreated from a moderate-to-heavy worm burden (hereafter referred to as group A), relative to the increased

[3] However, the results of the model are unaffected by this claim.

probability that drug resistance deprives a child of treatment who would otherwise go to a chemist or healthcare centre to alleviate a moderate-to-heavy worm burden (hereafter referred to as group B). Our model aims to capture this trade-off.

The probability that a treated child has a moderate-to-heavy worm burden is around 1.3% in areas where GiveWell-recommended deworming charities currently operate. We now need to know what proportion of treated people would not have access to deworming tablets in the absence of mass deworming. Addiss 2015 summarises the literature on the prevalence of unprogrammed deworming in worm prevalent locations, which ranges from 24% to 39% of school-age children, implying that 61% to 76% of children would not have access to treatment in the absence of mass deworming.[4] Further evidence comes from a recent mass deworming trial, an experiment in Busia, Kenya in 2004 (Miguel and Kremer 2004), where the control group in the experiment had a coverage rate of 5% (p.8). We use an average of the above studies to estimate that 24.4% of children would have access to treatment in the absence of mass deworming. This implies that each treatment has a 1.3% * (1 - 24.4%) = 0.98% probability of treating a child in group A.

We also need to estimate the probability that a given treatment increases the risk of drug resistance, and therefore reduces the efficacy of treatments for children in group B. As noted above, we estimate a 24.9% probability that deworming in 2022 leads to the development of drug resistance. However, unprogrammed deworming also contributes to the likelihood of drug resistance. We estimate that mass deworming contributes to 80.4% of deworming drug consumption, and we assume this is also the percentage contribution of mass deworming to potential drug resistance. Therefore, our estimated probability that *mass* deworming in 2022 causes drug resistance is 24.9% * 80.4% = 20.0%.

The proportion of children with access to deworming tablets in the absence of mass deworming is 24.4% (as noted above). We then multiply this number by the number of years until a new effective treatment would be developed, since resistance is long-lasting (p.1156) even after reductions in treatment volume. We make a rough approximation that this would be around 12 years, which is typically the minimum length of time (p.651) taken to develop and approve new medicines. Therefore, the probability that a given mass deworming treatment reduces the efficacy of treatment for a child in group B is 20.0% * 24.4% * 12 = 0.76%. Given a 10% reduction in treatment efficacy due to resistance (as noted above), this implies a 0.76% * 10% = 0.08% probability of reduced efficacy for a child in group B, scaled by the reduction in efficacy.

Overall, 0.98% of mass deworming treatments in 2022 are beneficial in the absence of drug resistance, compared to 0.98% - 0.08% = 0.9% of treatments once we account for the possibility of drug resistance. This implies a 0.08% / 0.98% = 7.7% reduction in cost-effectiveness. GiveWell's cost-effectiveness model includes a -4% adjustment for drug resistance risk. We slightly downgrade the cost-effectiveness of mass deworming by making a -7.7% adjustment.

[4] We restrict these figures to unprogrammed deworming that occurs outside of school-based programmes. Although school-based unprogrammed deworming occurs outside of national programmes and is therefore considered unprogrammed, it may still involve mass drug distribution.

Two implicit assumptions are made during this calculation. Firstly, it is assumed that rates of poverty and moderate-to-heavy worm burden do not change over time. A shrinking poverty rate would make potential drug resistance more detrimental, because in the absence of drug resistance, unprogrammed deworming would likely increase as more households are able to purchase deworming drugs. However, a lessened worm burden over time (due to improvements in economic development and hygiene) would make drug resistance less detrimental, because future households would have less need to purchase deworming drugs to stay healthy. These two factors have opposing effects.

Secondly, it is assumed that moderate-to-heavy worm burdens are no more or less prevalent among children receiving unprogrammed deworming. If children who purchase tablets from chemists are wealthier and have fewer moderate-to-heavy worm burdens, due to better sanitation for example, our model may overstate the potential harms of drug resistance.

An alternative model could explore a counterfactual scenario where deworming is targeted to individuals with moderate-to-heavy worm burdens to prevent drug resistance, which would require a rigorous costing of testing for the individual presence of worm burdens.

Sensitivity Analysis:

- If 40% of children receive unprogrammed deworming instead 24.4%, the reduction in cost-effectiveness is 14.2% instead of 7.7%.
- If the probability that mass deworming in 2022 causes drug resistance to occur is 40% instead of 24.9%, the reduction in cost-effectiveness is 12.4% instead of 7.7%.
- If the time taken to develop a new treatment is 20 years instead of 12 years, the reduction in cost-effectiveness is 12.9% instead of 7.7%.
- If the reduction in efficacy due to drug resistance is 20% instead of 10%, the reduction in cost-effectiveness is 15.5% instead of 7.7%.
- If all four of these parameters are adjusted as above, the reduction in cost-effectiveness is 76.2% instead of 7.7%. This implies that drug resistance risk can cause a substantial reduction in the expected cost-effectiveness of mass deworming if all four parameters are sufficiently high.

c) Sceptical Prior Opinion

GiveWell's and SoGive's Approaches to Interpreting Evidence:

SoGive and GiveWell both hold a sceptical prior opinion about interventions as a whole before investigating the evidence behind them. GiveWell's cost-effectiveness analysis scales down the economic benefits from follow-up studies to an experiment in Busia, Kenya, first to 13% of the original effect size, accounting for the possibility that published results may not reflect the true impact of deworming in that context ("replicability adjustment", row 11). Secondly, the effects are scaled down to 9-13% (depending on the charity) of the remaining effect size, which accounts for lighter worm burdens in currently targeted regions ("worm burden adjustment"). Thus,

GiveWell scales down the economic benefits to ~1% of the original effect size[5] to arrive at their estimate for the current effect of mass deworming, which is consistent with a sceptical prior opinion about the intervention as a whole.

In our correspondence with GiveWell, SoGive found that both organisations also agree that an even-handed approach should be taken on issues backed by sound evidence. For example, we would be willing to take the coverage rate reported in each study at face value. However, SoGive differs from GiveWell in its approach to interpreting the results from the long-run follow-up studies to the Busia experiment. On the issue of "economic losers" and the "black box problem", which we discuss here, GiveWell is more inclined to accept that the long-run earnings effects represent improvements in economic productivity, which benefit society as a whole. GiveWell's rationale is that their goal is to get a holistic best guess of an intervention's actual impact, which is generally more conservative than taking results from a study at face value, but not as conservative as looking at a worst-case scenario.

Implications for Economic Losers:

SoGive does not believe negative labour market externalities (i.e. "economic losers") are in fact a worst-case scenario. Rather, we think modelling the effects of "economic losers" is justified even while taking an even-handed approach to the evidence. This is motivated by the "black box problem", since the evidence predominantly points to mass deworming providing minimal short-run health, educational, or nutritional benefits, which raises some doubts about the likelihood that it leads to large gains in long-run productivity.

Two malaria eradication campaigns boost the plausibility of positive productivity effects from childhood disease eradication. Bleakley 2010 and Cutler et al. 2010 both find long-run jumps in income across entire birth-year cohorts born after the campaign. However, the *short-run* health effects of malaria prevention programmes are also far more established relative to mass deworming. We have not conducted thorough reviews of these long-run studies and their implications for mass deworming, although results from the Bleakley study were robust to re-analysis.

[5] I.e. the original effect size is multiplied by 13% (replicability adjustment) and somewhere between 9% and 13% (worm burden adjustment).