

# Worms, wisdom, and wealth: why deworming can make economic sense

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**For those of us who have had worms, getting rid of them seems a good idea, and multiple studies demonstrate the simplicity and benefit of deworming children. In the past decade or so, there has been a dramatic increase in efforts to provide inexpensive deworming medications, but at the same time there have been calls to re-evaluate the impact of deworming programs. In this review, we examine the history of deworming and explore the evidence for effects of deworming on health, on child development, and on economic returns. Important policy conclusions include that a paucity of randomized trial data suggesting benefit does not equate to a lack of benefit and that a greater emphasis on documenting such benefit should be pursued.**

## A little history

Large-scale deworming programs emerged as popular (and populist) programs at the beginning of the 20th century, and their popularity has grown as treatment and program design have become more efficient and better understood.

### *High profile, early success in the USA*

At the beginning of the 20th century, the Rockefeller Sanitary Commission, later to evolve into the Rockefeller Foundation's International Health Board, began its humanitarian work in the USA by examining claims that the wealth disparity between North and South was accompanied by similar disparity in health and that worm infection in particular might be a cause of underdevelopment. Hookworm, then infecting 40% of Southern school children examined, was identified as the 'Germ of Laziness' [1], a phrase from the early days of germ theory, which might today be translated as 'an infectious agent resulting in a reduced ability to work or study'. In response, the Commission initiated large-scale, population-based treatment (using oral thymol) and hygiene education programs [2,3].

Remarkably, the Commission also implemented comprehensive monitoring and evaluation programs that measured both health and education outcomes, and subsequently reported important effects on anemia and education over the 5 years of the intervention. So good was the record-keeping that some 100 years later a comprehensive re-analysis has been possible. Bleakley [4] has assessed the

contemporaneous effects of deworming on health and education outcomes as well as long-run effects on adult earnings [by projecting geographical panels (cohorts) forward 50 years]. These results confirm the contemporaneous observations and show that school age children in areas with higher hookworm infection showed greater increases in school attendance and literacy measures after intervention. No significant effects were found in adults. The difference-in-difference follow-up of long-run cohorts indicates both a marked increase in education quality (rather than quantity) and a substantial income gain in the most heavily infected populations. The scale of effect is such that the hookworm infection rate may have accounted for around half of the literacy gap and up to 20% of income differences between the North and South of the USA at the time of the study.

The results of the Commission were interpreted as suggesting an important role for worm infections generally, and were followed by Rockefeller-supported campaigns in several low-income countries. Although the deworming campaign in the USA was among the last to be conducted in a high-income country and was followed by a lull in interest in these diseases of the poor, interest in these diseases resurfaced on the public health agenda as a result of the Second World War.

### *Deworming 'This Wormy World' in 1947 – not an option*

When the President of the American Society of Parasitology entitled his inaugural address 'This Wormy World', he was reacting to an important post-Second World War phenomenon [5]. In his words, ex-servicemen were coming '...back from the Pacific...to homes widely dispersed throughout the [continental USA]...to live a lifetime in familiarity with the strangely sounding names of their distantly-acquired helminthiases'. A similar phenomenon was also being experienced in Europe [6–8].

Stoll lamented that the treatment control 'tools...are in need of sharpening' and lists the most effective anthelmintics then as hexylresorcinol, chenopodium (fern extract), and tetrachlorethylene – all characterized by poor efficacy and worrisome toxicity. Suddenly, the diseases of the poor were arriving in the lands of the rich and the available treatments were largely ineffective.

### *New approaches to deworming lead to new policies*

Stoll's call for a world-wide effort to control worms was not possible with the tools then available, but would resonate

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over the following decades as new drugs and new program designs began to emerge.

Three developments converged to bring deworming back on to the agenda. First, the steady emergence of new anthelmintic drugs – particularly benzimidazoles – with greater efficacy and better safety profiles prompted the WHO to re-activate a program of research and control in human intestinal protozoan and helminthic infections [9]. These drugs are considered safe enough to be delivered without individual diagnosis [10], and a recent systematic review of Randomized Controlled Trials (RCTs) shows that they are highly efficacious in terms of cure rate and, even more so, in reducing infection intensity and thus transmission [11].

The second development was the application of ecological theory to helminthic diseases [12,13], from which emerged new evidence that worms could be controlled much more cost-effectively by programs designed to take advantage of the population dynamic characteristics of macroparasites, such as age-specific infection, overdispersion, predisposition, and transmission externalities [14,15].

The final development was a shift in public health perspective with the growing success of child survival programs [16], and the recognition that the successful efforts to reduce mortality needed to be supplemented by efforts, such as deworming, aimed at supporting the continuing development of surviving children, especially through a more integrated and multisectoral approach to public health [16–18]. This human development agenda was the prime motivation for the highly successful national deworming programs in Japan and Korea.

The convergence of these three key developments led to significant changes in international policy. The WHO gave greater emphasis to deworming in specific age groups, especially preschool children, school age children, and women of reproductive age [19], and in 2001 the World Health Assembly declared the explicit goal of ensuring that 75% of all school age children in endemic areas received treatment (see: [http://www.who.int/neglected\\_diseases/mediacentre/WHA\\_54.19\\_Eng.pdf](http://www.who.int/neglected_diseases/mediacentre/WHA_54.19_Eng.pdf)). In addition to recognition of the benefits for health, UNICEF made a specific connection between deworming and the promotion of child development [20]. At the World Education Forum in Dakar in 2000, several agencies, including UNESCO, UNICEF, WHO, and the World Bank, launched a consensus framework to Focus Resources on Effective School Health (FRESH) that specifically included a school-based approach to deworming as a contribution not only to health but also to better education and child development [21].

An additional key aspect of this policy success was the formal commitment of the private sector to efforts to deworm the world's children. Following a trend first established in the 1980s by Merck in their Mectizan donation for onchocerciasis [22], pharmaceutical companies have now donated treatment specifically for deworming of school age children: with 50 M mebendazole treatments a year from Johnson & Johnson in 2007, rising to 200 M in 2010, and 400 M treatments of albendazole from GlaxoSmithKline in 2012 (see: [http://www.unitingtocombatntds.org/downloads/press/ntd\\_event\\_table\\_of\\_commitments.pdf](http://www.unitingtocombatntds.org/downloads/press/ntd_event_table_of_commitments.pdf)).

These donations have had broad impact, increasing the cost-effectiveness of deworming and heightening the attractiveness of deworming programs within public health systems.

These international developments in policy and technology led to dramatic increases in the number of individuals receiving deworming medications around the world and were underpinned by a growing body of evidence assessing the benefits of deworming.

### The effects of worm infection and the consequences of deworming

Multiple studies have explored the impacts of worms on health, the consequences for the physical and intellectual development of children, and the long-run effects on individuals. Below we summarize the existing evidence and discuss some of the strengths and limitations of these data. The evidence includes traditional medical trials, but there is also important evidence from other methods and evidence in the social science literature, particularly economic literature, to be considered.

#### Evidence from medical trials

The Cochrane Library has recently published a systematic review of randomized controlled trials of deworming [23], using well-validated methods and expanding upon a previous systematic review [24]. The Cochrane Collaboration is a well-respected source of information for evidence-based decision-making for medical interventions, combining systematic search methods with strict selection criteria in order to minimize bias and enhance objectivity. The review concludes that available evidence suggests significant benefit of deworming on both weight and hemoglobin in children with confirmed worm infection. The authors note that there were not sufficient quality data available to determine the effect of deworming on cognitive function in children with worms. These findings are important because they support the efficacy of deworming for improving nutritional and hematologic outcomes in children with worms.

However, the review also analyses data from studies of populations empirically treated for worms, where many of those treated were likely to be uninfected. The review concludes in the abstract, ‘it is probably misleading to justify contemporary deworming programs based on evidence of consistent benefit on nutrition, hemoglobin, school attendance or school performance as there is simply insufficient evidence to know whether this is so’. Some authors have subsequently interpreted this conclusion as suggesting that the benefits of routine deworming policies may need to be re-evaluated (see: ‘Deworming: not all it’s cracked up to be?’ <http://blogs.plos.org/speakingofmedicine/2012/07/18/should-deworming-policies-in-the-developing-world-be-reconsidered/>; <http://www.thecochranelibrary.com/details/editorial/2477681/Debating-the-evidence-for-deworming-programmes.html>), whereas others independent of the review have emphasized its potential limitations as a method to inform or justify policy decisions (see: ‘Deworming should remain an essential cornerstone for NTD control’ <http://blogs.plos.org/speakingofmedicine/2012/07/18/should-deworming-policies-in-the-developing-world-be-reconsidered/>).

reconsidered/; <http://www.thecochranelibrary.com/details/editorial/2477681/Debating-the-evidence-for-deworming-programmes.html>; <http://blogs.berkeley.edu/2012/07/20/cochranes-incomplete-and-misleading-summary-of-the-evidence-on-deworming/>). In trying to balance these conflicting conclusions, here we examine some of the limitations to the Cochrane review, several of which are highlighted in the review itself. Two particular issues are discussed below.

First, the included studies were not designed or powered to be able to answer the question asked. All of the population deworming studies the review included had significant issues related to study design, sample size, follow-up duration, and risk of other forms of bias. For example, the length of follow-up in many studies may have been insufficient to document differences in the outcomes measured. In 18 out of 42 studies, the duration of follow-up was 6 months or less, with 4 studies having a month or less of follow-up. In addition, over half of the studies (23 out of 42) were classified as having a high risk of bias in at least one domain (selection bias, performance bias, detection bias, attrition bias, reporting bias, or other bias). In fact, only one trial [25] was classified as having low risk of bias across all domains; and these data were not included in the meta-analysis. When applying the GRADE criteria to the included studies, the authors found that the quality of the evidence assessing all outcomes was ranked very low.

In addition, the population studies may not be addressing the right question (see also [26]). The latest review concludes that treating worm-infected people has benefits, but that the studies of empirically treating populations (which include uninfected people) are problematic in terms of both quality and outcomes. However, the rationale for population deworming (where everyone is treated, infected or not) is based not on the expected benefit of the intervention in those who are uninfected, but on the fact that empiric deworming programs are more cost-effective and pragmatic than screening and treating. The systematic review showed significant benefit for several outcomes for populations of infected people, but when the uninfected population is included it dilutes the potential impact of the intervention and dramatically affects the power of these studies to detect meaningful differences in the outcomes they aim to document.

In addition to these issues, there are important limitations of pooling randomized trial data for the evaluation of large empiric deworming programs. Traditional randomized controlled trials often use restrictive inclusion criteria to ensure that the population being evaluated has clearly defined baseline disease categorization, homogeneous exposure risk, and similar measurement of outcomes. Participants in large-scale school-based deworming programs are highly heterogeneous. Many, if not most, are not infected with helminths, and among those with helminth infection, disease burden is highly variable. In addition, there may be important sociodemographic and clinical differences in individuals that impact the magnitude of benefit from deworming [27]. Although randomization should homogenize the population, in practice, this may not be achieved in small studies of the kind reported in the Cochrane review. Subgroups of individuals who are malnourished, co-infected with other pathogens, or who lack

access to clean water and sanitation, may respond differently to deworming. The inclusion of a broad representation of populations does increase the generalizability when assessing impact, but may result in failing to document important benefits among these subgroups of individuals [28].

The Cochrane review is helpful as it details the limitations of pooling the available evidence as described above. However, given the limitations of these data and the multiple studies documenting benefit of deworming, a summary of selected data related to specific benefits of deworming is included below. This includes not only traditional medical trials that the Cochrane approach is well suited to analyze but also other sources of evidence that are helpful for our understanding, including social science trials, particularly from the economic literature.

#### *Mortality and clinical consequences of infection*

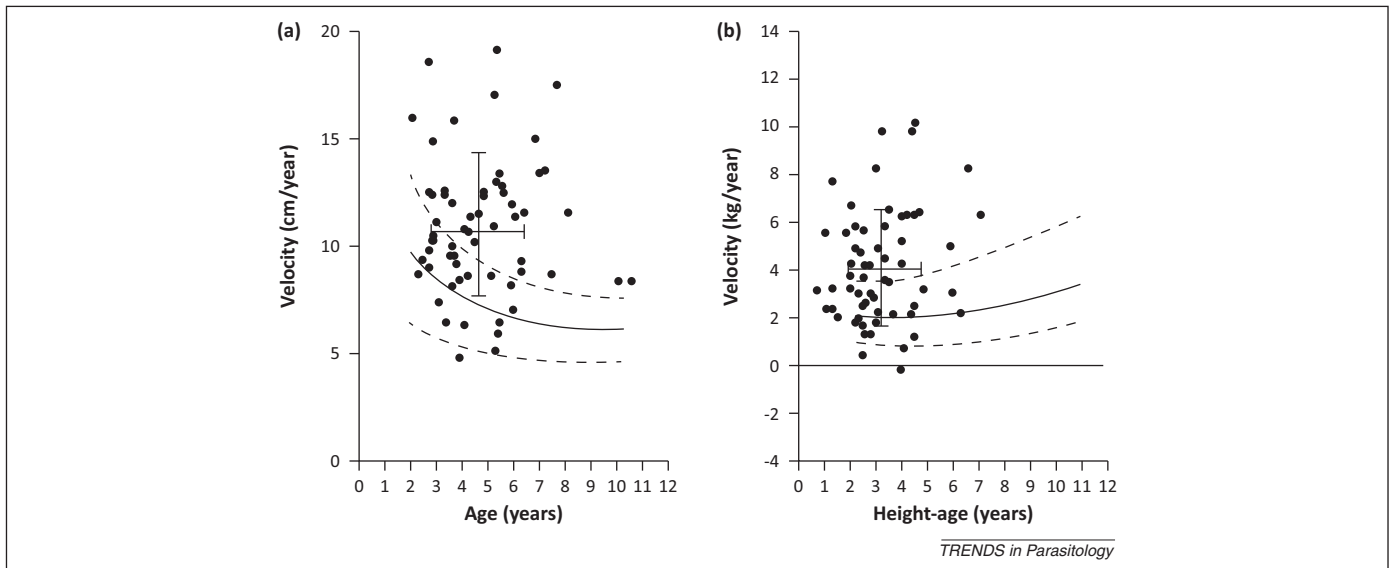
Worm infections can be associated with severe and fatal syndromes, including the severe anemia of necatoriasis, obstructive ascariasis, and the colitis of trichuriasis syndrome [29–31]. These conditions are associated with intense infections which are typically rare, but may become epidemic following social shocks, such as described in Rangoon and in post-Second World War Darmstaedt [32,33].

However, estimating the impact of worm infections on mortality has proved difficult. Most studies of population mortality from soil-transmitted helminths have involved estimates of mortality from communities in unusual circumstances (as in the Darmstaedt epidemic) or hospital populations, and offer little guidance as to the direct and indirect population effects. The only RCT that has been adequately powered to examine the impact of deworming on mortality showed little effect in a lightly infected preschool population in north India [34]. This was a large community-based trial and although this does not rule out effects on mortality in other populations, such effects are likely to be small.

The dramatic consequences of infection, and relatively immediate benefits of deworming, observed here probably represent outliers in a distribution more typically characterized by a more insidious process. Worm infections are typically chronic, with infection and reinfection occurring throughout the development of a child [35]. The chronic insults – for example, sustained blood loss and inflammation – have cumulative consequences, measureable in terms of growth and physiological status. The benefits of deworming would be expected to be modest (on average) and measurable only over relatively long periods of follow-up, as benefits accrue slowly with the reversal of deficits and the prevention of further insult.

#### *Health, physical growth, and deworming*

Worm infections commonly affect the gastrointestinal tract, with potential adverse consequences for nutrition and absorption [36]. As a result, the impact of worm infections on growth and development is a major concern. One of the more dramatic observations of the effect of deworming on children is the ‘catch up’ growth exhibited with treatment for trichuriasis dysentery syndrome



**Figure 1.** Growth velocities of children in Jamaica with *Trichuris* dysentery syndrome. Height velocity is shown in (a), and weight velocity in (b), measured over the half year following their treatment [38]. The ages of the children are shown at the midpoint of the interval over which their growth velocities were calculated. In (b), age has been converted to height-age, that is, the age of the median reference child of the same height as the subject, to show weight growth as related to height, an indication of the change in body habitus (leanness or stoutness) of the subject (see appendix of [37]). The unbroken line is the median of the standards for growth velocity, and the broken lines are 2 SD above and below the median.

[37,38]. Such children are stunted (short for age), and following deworming can achieve near-expected height-for-age and weight-for-age as a result of catch-up growth rates more than 2 SD above Tanner–Whitehouse standards [39] for growth velocity (Figure 1).

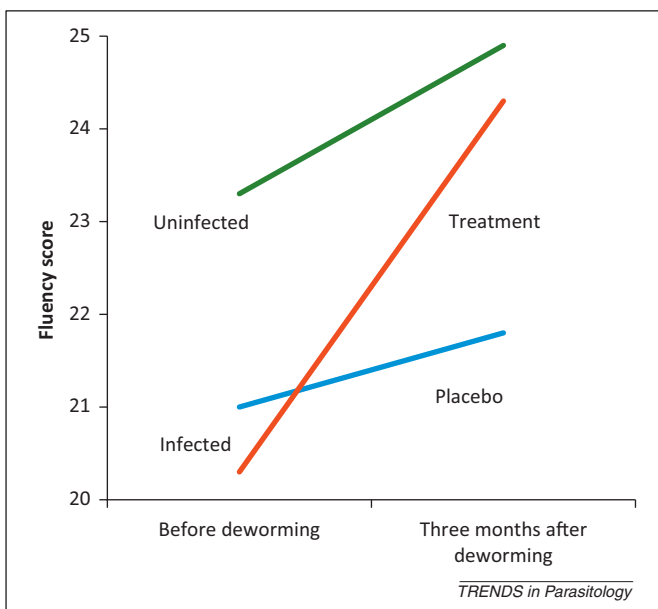
#### Cognition, education, and deworming

In addition to direct effects on health and growth, worm infections are also associated with other significant societal impacts, including cognition and school attendance. A

particular challenge in comparing the outcomes of cognition studies is the absence of a consistent test battery to allow comparison between studies; in fact, most studies use different tests which measure different cognitive domains. It has also been suggested [40] that it may be difficult to prevent reinfection long enough for cognitive benefits to accumulate in a test environment and that tests should focus on the rate of acquiring skills. The Cochrane review (see above) concluded that there is insufficient evidence to suggest clear and consistent benefit of deworming on these outcomes. However, whereas some studies report no effect of deworming on cognition over the total population studied [41–45], significant improvements in cognition have been observed among the most vulnerable of the children: the youngest of primary school children in China [44] and undernourished children in Jamaica [41].

In one study in Jamaica (Figure 2), cognitive scores in infected children were lower than in uninfected children, perhaps reflecting socioeconomic differences between uninfected and infected children as mentioned above. Treatment of one cohort of the infected children improved their cognitive scores over those who remained infected and untreated. The improvement in score was such that the treated children were not significantly different from those who were initially uninfected, implying that treatment alone allowed them to catch up with their better-off peers [46]. A longitudinal study in Zambia, using a cognitive test battery to establish an ability test score, showed that the longer that deworming and school health treatment continued, the greater the improvements in skills and the quicker mastery of the skills [47].

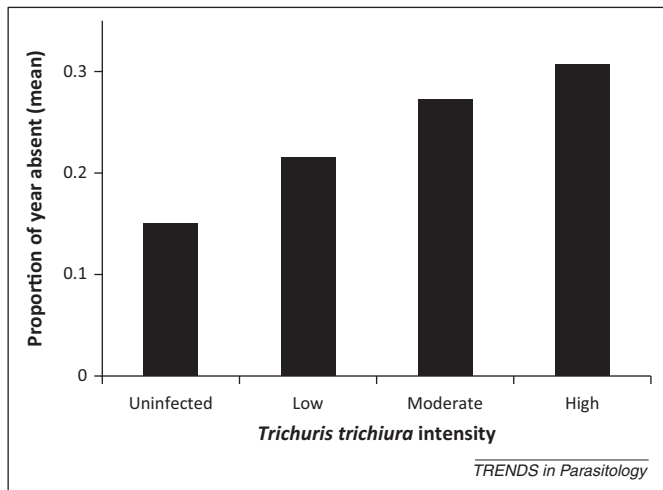
In addition to cognitive benefits observed in some studies, several studies have also shown that school children infected with worms are absent more frequently than those uninfected. For example, in one study of school children in Jamaica the intensity of *Trichuris* infection was correlated with school attendance (Figure 3), and a correlation was



**Figure 2.** Performance on cognitive tests following deworming. Treated children improved in cognitive scores over those who remained infected, catching up to those who were uninfected [46]. The figure plots mean fluency test scores pre- and post-deworming in a study among school children (9–12 years of age) in Jamaica. The test showed a significant improvement in the treatment group over and above the placebo group and uninfected control group. The improvement observed in each group is presumed to be due to the effect of practice.



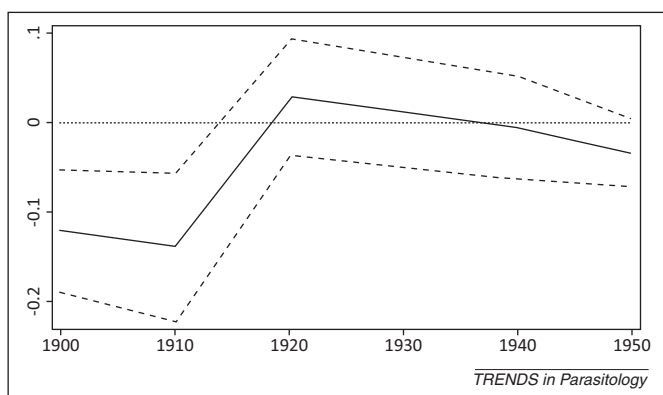
## Review



**Figure 3.** School children infected with worms were absent more frequently than those uninfected. The figure plots the proportion of year absent from school in children in Jamaica with different intensities of *Trichuris trichiura* infection estimated by fecal egg counts (eggs/g: 0 = uninfected, 1–2000 = low intensity, 2000–7000 = moderate intensity, >7000 = high intensity) [55]. All infected, and heavily infected, children were absent from school significantly more frequently than uninfected children (analysis of variance:  $F = 23.78$ ,  $P < 0.0001$ ).

also found between absenteeism and hookworm infection in the Southern USA (Figure 4).

Given that worm infections also correlate closely with poverty, it is possible that the effects of worms on school attendance are a result of confounding by socioeconomic status. Separating causality from association requires evidence that deworming alone would result in reduced absenteeism. An RCT in western Kenya has shown that biannual deworming resulted after 1 year in significant differences in infection levels (25% of pupils had serious worm infections in treated schools, 52% in untreated) and, along with self-reported improvements in health, school participation had increased by 7% and absenteeism decreased by 25% [48]. Interestingly, the analysis of data



**Figure 4.** School attendance before and after treatment in the Southern USA. Pre-deworming, areas of high hookworm infection in the American South had lower school attendance than areas with lower hookworm infection, but following deworming that started circa 1910, school attendance in the high infection areas surged and converged with attendance in lower infection areas [4]. The census year from 1900 to 1950 is displayed on the x-axis, whereas the y-axis plots year-specific coefficients (unbroken line) with confidence intervals (broken lines). For each year, school attendance is regressed on preintervention hookworm infection and demographic controls to estimate the coefficient.

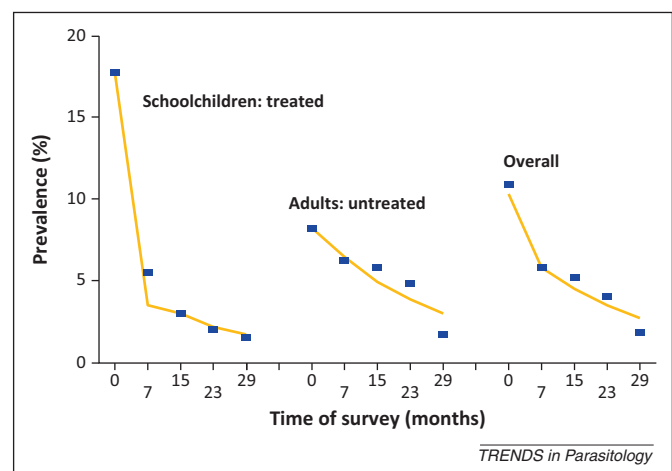
from the Southern USA shows a similar magnitude of change: before deworming, areas of higher hookworm infection had lower school attendance, and after deworming, school attendance in these areas surged and converged with attendance in other areas (Figure 4) [4].

#### Long-run benefits of deworming

Although the health and education benefits of deworming may be the particular concerns of the human development sectors, the larger issue for development is whether these benefits translate into tangible gains for individuals or society over time. A particularly relevant outcome in this context is earnings. We have already seen that the Rockefeller Campaigns at the beginning of the 20th century had long-run benefits for those in the USA, but can we detect similar benefits today for those in low-income economies?

Only one study has addressed these economic impacts prospectively (S. Baird *et al.*, unpublished). In this study in Kenya, the investigators conducted follow-up of adults who had been dewormed as school children 10 years earlier [48]. Approximately half of these young adults (aged 20–26 years) had been treated in school some 10 years previously. The treated population had significantly better self-reported health, but no differences in body mass index (BMI) or height. Despite the lack of direct effect on nutritional parameters after 10 years, primary school participation increased significantly in the treated population (0.129 years), as did years enrolled in school (nearly 0.3 years). There were small, non-significant gains in vocabulary knowledge and exam passing rates, with significant improvements observed in the subsample of respondents who were no longer in school at the time of follow-up. Overall, their human development measures seemed only modestly improved.

Additionally, the adults in the treatment group ate 8% more (equivalent to an additional 0.1 meals/day) and worked 4.65% more hours on average (an additional 1.53 h). Among wage earners, this translated into 5.2 more



**Figure 5.** Treatment of children reduced infections in adults. With mass school-based deworming, worm burden in untreated adults fell by nearly 50% [14]. The figure plots age-standardized estimates of the prevalence of *Ascaris lumbricoides* infection in the target (2–15 years), adult (>16 years), and overall population, in a study on the island of Montserrat. Infection data are from the initial survey, and from surveys conducted after two and four cycles of treatment. Reductions in prevalence were observed not only in the target age class of 2- to 15-year-olds, but in adults as well, even though less than 4% of adults received treatment.

hours worked per week among wage earners, and an increase in earnings of 25.3 log points. Furthermore, those in the treatment cohorts were more likely to have acquired better paid jobs: men were three times more likely to be employed in manufacturing, and women more likely to be in wage labor than casual labor. Average adult earnings among those working for wages rose over 20% (which is almost identical to the USA study [4]). Similar, although slightly smaller, effects were also seen as externalities in those who had attended schools within 6 km of treated schools, in terms of meals eaten labor supply in wage earners, and labor earnings.

Overall, this study suggests that deworming may create an average increase in labor earnings of over 20% for wage earners. When treating increased hours as a gain in endowment, the estimated social financial rate of return is around 65% per year.

### Externalities

An important epidemiological observation regarding deworming is that infection intensity is often greatest in school age children. This age distribution is most marked for *Ascaris* and *Trichuris*, where some 70% of all worms may be in this age group, and less so for hookworm where adult infection may also be common. As a result of this distribution, treatment of school age children alone has a disproportionate impact on the number of parasite eggs shed into the environment, and hence on the transmission in the community as a whole (Figure 5) [14]. This effect was also observed in the Kenya study, where both infection and school absence were reduced in untreated children in treatment schools, and in children in untreated schools within 6 km of treatment schools [48]. This phenomenon has also been used to explain the observation that the preschool siblings of children in treatment schools showed improvements in cognitive performance equivalent to half a year of schooling, and that the effects were twice as large for preschool children with siblings at school (O. Ozier, unpublished).

This epidemiological phenomenon has important practical consequences because treatment of an easily accessible portion of the population benefits even those that remain untreated. In economics, this is termed an externality and is in effect a free benefit from the investment in those treated, analogous to the herd immunity benefit from vaccination. Note that other externalities of deworming are also claimed, such as concurrence with malaria [49,50] and exacerbation of HIV transmission [51–53], which if true would further enhance the benefit–cost ratio of deworming.

### Accessing the social sciences literature

When reviewing this paper, some of our medical peers expressed surprise, even concern, that we cited unpublished observations. In fact, in both cases, these observations are from working papers that have been posted for at least 2 years on the websites of academic institutions to allow open access and open peer review in advance of submission, as is normal practice in the economics literature. We cite these studies here as unpublished following the style of medical journals and

reflecting the wide gap in the conventions between these two disciplines.

### Concluding remarks

Mass deworming among populations at risk of worm infections is safe, effective, and practical, and is more cost-efficient and programmatically feasible than screening and treatment of infected individuals. The additional benefit (externality) of reducing transmission in the community as a whole is alone sufficient to justify full subsidy as a public good, especially as cost-recovery efforts have been found to decrease take-up by 80% [54].

The cost-efficiency of deworming in the 21st century has been further enhanced by reductions in the costs of drugs and their delivery. As a result of donations, deworming drugs are now available at zero purchase cost. Delivery costs have been significantly reduced by delivery at the margins of health systems, such as community-directed or school-based Mass Drug Administration (MDA) programs.

The benefit–cost ratio of deworming is perhaps best shown in development rather than health terms, and in the case of education access, for example, the US \$3.50 cost per additional year of school participation exceeds the cost-effectiveness of other methods of increasing schooling [48]. Where economic analyses have assessed long-run benefits, they have concluded that deworming at school age enhances earnings in adulthood (S. Baird *et al.*, unpublished) [4].

In terms of health, the available evidence suggests that deworming benefits infected children in terms of improved growth and reduced anemia. Attempts to use the Cochrane processes to assess whether these benefits continue to accrue during population-based deworming provide mixed results, apparently reflecting both limitations in the ability to detect modest (on average) development gains, especially when a substantial proportion of the population is uninfected, as well as a lack of high quality longitudinal data. The benefits of deworming are most apparent in the long-run studies that assess outcomes in terms of accumulated impacts on broad measures of human development, studies that are more common in the epidemiological and social sciences (economics) literature. The large and long-term MDA programs that are being launched for various helminthiases as part of the Neglected Tropical Diseases efforts provide an important opportunity to accrue higher quality data to inform policy in the future.

An important policy conclusion, however, is that a paucity of randomized trial data suggesting benefit does not equate to data suggesting a lack of benefit. For the hundreds of millions of children growing up at risk of helminth infection globally, the potential benefits of deworming during childhood should not be ignored, even while a greater emphasis on documenting such benefit is pursued.

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