BEST PRACTICE PAPER: NEW ADVICE FROM CCo8

DEWORMING

Andrew Hall & Sue Horton

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Deworming

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Cover image credit: Andrew Hall, Westminster University

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PREFACE

For two years before Copenhagen Consensus 2008, a team of experts wrote papers identifying the best ways to solve the world's biggest problems.

Those papers showed that we have the knowledge to do tremendous amounts of good in each of these areas.

That research was utilized by a panel of top economists, including Nobel laureates, who were commissioned by the Copenhagen Consensus Center to identify the most effective investments.

The prioritized list produced by Copenhagen Consensus 2008 provides governments, donors and philanthropists with a guide to the areas where relatively small amounts of money can prove extremely powerful.

The research that provided the building blocks to this process – and a full description of the outcome – form the book, 'Global Issues, Global Solutions, Volume Two', published by Cambridge University Press in 2009. This is an excellent overview of global problems and the most promising solutions.

Given the level of interest in Copenhagen Consensus 2008, the Copenhagen Consensus Center decided to commission a specific set of papers that deal with the spending options given highest priority by the expert panel.

The goal of these Best Practice Papers is to provide clear and focused empirical recommendations on the costs and benefits of implementing the solutions, and advice on how to do so.

The problems dealt with by Copenhagen Consensus 2008 are vast. The practical approaches identified here prove incredibly powerful reading. The Copenhagen Consensus Center hopes that they shall prove an invaluable resource, and further advance the goal of promoting the most sound investments to help humanity.

Bjorn Lomborg
Copenhagen, 2009

EXECUTIVE SUMMARY

The prevalence of infection with at least one species of intestinal nematode worm, which include roundworm, hookworm and whipworm, is estimated as 48% in developing countries. Sub-Saharan Africa, South and Southeast Asia (including the Pacific islands), and parts of Latin America are most heavily affected. Transmission depends on sanitation, agricultural practices, whether or not shoes are worn, and environmental conditions. Although infection is widespread, the number of individuals with a moderate worm load (defined here as 10 or more worms) is not substantial until the prevalence exceeds 50%.

Mass treatment is safe and inexpensive. Albendazole and mebendazole can be given as single-dose treatments to children aged two years and older, and there are preparations available for children aged 1 – 2 years. The cost of delivering one round of treatment is approximately $0.15 per child for children when administered in school, and $0.25 per child for preschool children when combined with another intervention in programs such as Child Health Days or in primary health care facilities. Treatment is recommended for children aged 2 through 14 years if the prevalence in the country or region exceeds a specified threshold.

In 2006 the World Health Organization (WHO) revised its guidelines regarding such thresholds and now recommends treatment once a year where infection rates with any intestinal worm exceed 20% and twice a year where they exceed 50% or up to three times a year if resources permit. Estimates of the prevalence of infections with intestinal nematode worms indicates that this would give an annual global treatment cost of $276 million for the developing world but excluding the former members of the Soviet Union, for which prevalence data are not available.

An analysis of the relationship between the prevalence of infection and the estimated proportion of individuals with 10 or more worms, which might be considered as a moderate to heavy infection, indicate that a threshold prevalence of 20% for mass treatment is not cost-effective when estimated in terms of cost per diseased person treated. We propose alternative thresholds: treatment once per year where the prevalence is 40% or more, twice per year where it is 60% or more, and three times per year where it is 80% or more. This would have the benefit of lower cost than current WHO recommendations ($224 million annually) and devotes a higher proportion of expenditures to treating individuals who are infected (74% as opposed to 61%), and a higher proportion to treating individuals with 10 or more worms (31% as opposed to 21%).

Treatment is very cost-effective. In schoolchildren, the reduction in anemia in particular due to treating hookworm is associated with increased school participation and hence school achievement, and ultimately with increased productivity of working-age adults. In countries with a high prevalence of infection, the benefit:cost ratio may be as high as 60:1 (although this would be reduced somewhat if costs of hiring additional teachers were taken into account). For preschool children, there are fewer studies. Estimates suggest however that the benefits of reduced anemia could give benefit:cost ratios of 6:1; this does not include additional gains due to better weight and height gains.

The paper also makes some recommendations for the future. First, it would be good practice to alternate between different classes of deworming drugs to help avoid developing drug resistance: mebendazole/albendazole could be alternated with pyrantel/oxantel for example, although this would require changes to the WHO Essential Drugs list. Second, it is good practice to do sample surveys of prevalence in schoolchildren at least once every two years. Simple non-quantitative tests cost about 0.1% of the cost of treatment (the estimate is less than $0.25 million worldwide), and can save money by eliminating unnecessary treatments. Third, given that treatment thresholds are based on the combined prevalence of infection with any species, more work is needed on estimating the prevalence of mixed infections as current global data are published by species.

In the Copenhagen Consensus 2008, a panel of renowned economists ranked five nutritional interventions among the top ten of 30 proposals to answer the question, what would be the best ways of advancing global welfare? Deworming and other nutrition programmes in school were ranked as the sixth best intervention overall, considering their potential benefit:cost ratio, anticipated feasibility and the sustainability of the intervention.

In Section 1 we discuss briefly the challenges involved in controlling disease caused by intestinal nematode worms, particularly roundworm (*Ascaris lumbricoides*), whipworm (*Trichuris trichiura*) and the two main species of hookworm (*Ancylostoma duodenale* and *Necator americanus*). In Section 2 we discuss how to treat disease and start to reduce transmission by deworming people using inexpensive, single-dose anthelmintic drugs with the focus particularly on school-age children, but with some discussion of treating preschool children and pregnant women. Section 3 provides some cost-effectiveness and economic analysis. Section 4 concludes.

1 THE CHALLENGE

It has been estimated that 1.22 billion people in low, lower-middle and upper-middle income economies, or 26% of their population, are infected with roundworms, 0.80 billion (17%) with whipworms and 0.74 billion (15%) with hookworms (de Silva *et al.*, 2003a). From these prevalences it can be estimated that some 2.3 billion people, or about 48% of people living in the world's poorest countries are likely to be infected with at least one of these types of worms and that nearly 10% are infected with two or more types, if we assume to a first approximation that infections are independent (see Hall *et al.*, 2008 for further discussion). Figure 1, from de Silva *et al.* (2003a), shows the distribution of these three common types of intestinal worms. The countries of sub-Saharan Africa, South and Southeast Asia and parts of Latin America are worst-affected, which reflects environmental conditions that suit the survival of infectious stages, poor sanitation, poor personal hygiene and perhaps particular behaviours that increase the risk of infection, such as using fresh human faeces as a fertilizer or not wearing shoes to protect from infection with hookworm. There may also be considerable variation in the prevalence of infection by region, within countries, and even within different regions of the same country, largely depending on local environmental conditions. For example the distribution of infections varies with altitude, probably as a result of the effects of temperature, humidity and ultra-violet light on the survival of worm eggs and larvae, while in crowded urban slums there may be intense transmission of roundworms and whipworms.

Infection with intestinal worms is not necessarily the same as disease. This is because the risk of being diseased depends principally on the number of worms in the gut, commonly called the worm load, but also on the species of worm, the mixture of species, the duration of infection, and the size, age and health of the infected person (Hall *et al.*, 2008). Worm loads tend to accumulate slowly because each worm within a human host is the result of exposure to a single worm egg or larva; because worms can live for 1 – 3 years, depending on the species; and because there seems to be no fully protective immunity, so infection is a continuous process and disease can develop slowly.

Infections are usually diagnosed using a microscope to see the characteristic worm eggs in a faecal sample. The proportion of people with eggs in their faeces provides an estimate of the prevalence of infection, but this is a poor indicator of the risk of disease and of the impact of treatment because only two worms – a male and a female – are necessary to produce eggs, and two worms are very unlikely to cause disease. The concentration of eggs in faeces can be used as a proxy for the worm burden, but there is evidence that egg counts per female worm vary from country to country, for roundworms at least (Hall & Holland, 2000).

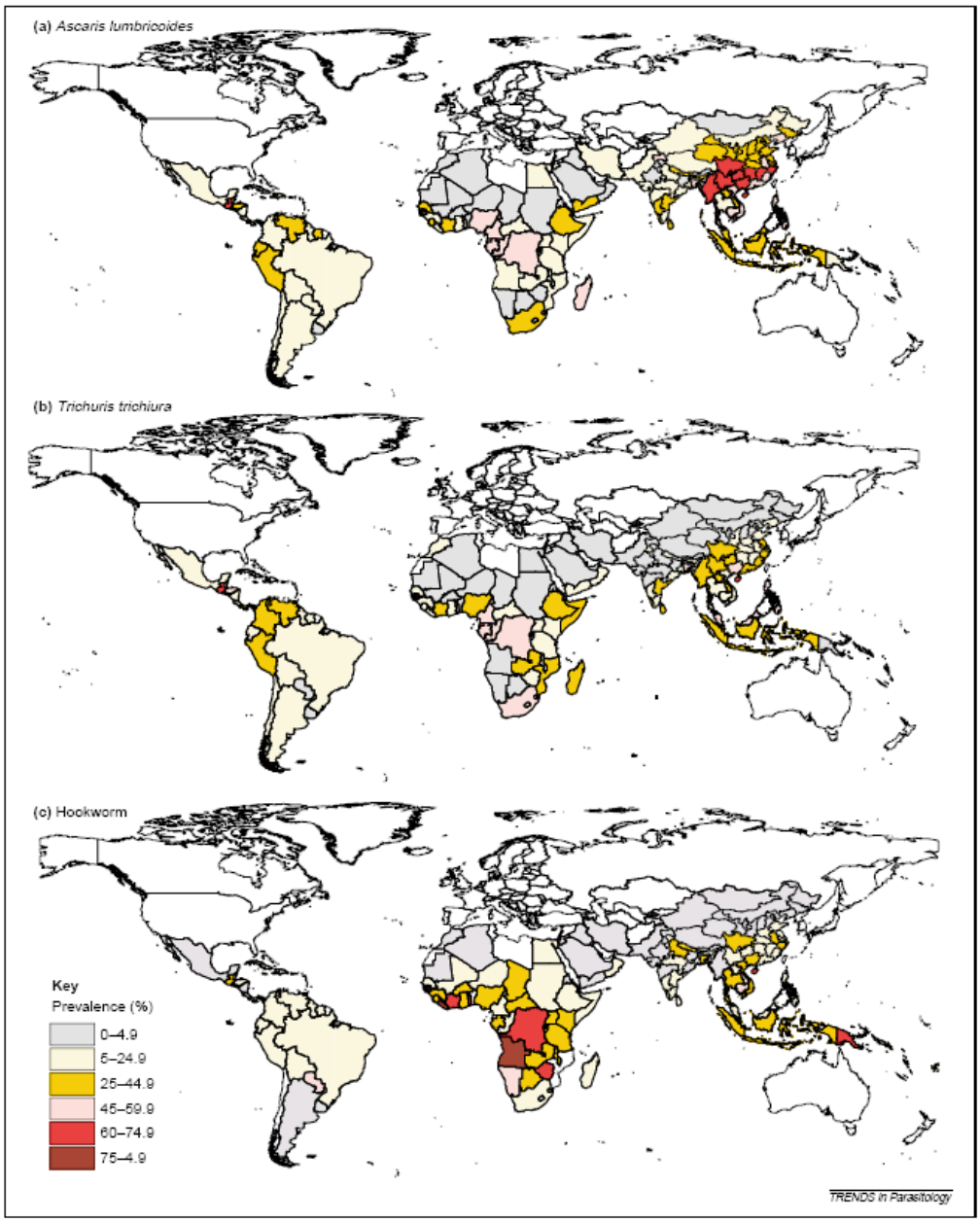

Figure 1. The global distribution of (a) *Ascaris lumbricoides*, (b) *Trichuris trichiura* and (c) hookworm. White areas represent countries not included in the present analysis. Data obtained from http://www.fic.nih.gov/dcpp/dcp2.html

http://parasites.trends.com

Figure 1 The distribution of *Ascaris lumbricoides*, *Trichuris trichiura* and the hookworms.

Source: de Silva *et al.* (2003a)

The risk that a few worms can cause disease is very low; disease is mostly associated with moderate to heavy infections. Although there is no accepted number of worms that defines moderate to heavy infections for each species, it is typical to find >80% of worms in <20% of hosts (Anderson & May, 1991). The consequences are: that not all infected people will benefit from treatment to the same degree; that any measured effects of treatment on the

moderately- to heavily-infected minority may be diluted in the average; and that it may not always be cost-effective to treat the whole population when only a few individuals are diseased.

The worm burden is a better indicator of the risk of disease than the prevalence, but estimating the burden either requires expelling and counting worms, which is difficult to do, or requires an estimate of the egg count, which is highly variable. Unfortunately the prevalence cannot readily be used to estimate the mean worm burden because the relationship between the two is highly non-linear. Figure 2 shows that when the prevalence of roundworms is below about 50%, the mean worm burden is 2 or less, but above a prevalence of 50% the mean worm burden rises exponentially. This means that the proportion of people with moderate to heavy infections who are at risk of disease rises similarly (Guyatt & Bundy, 1991).

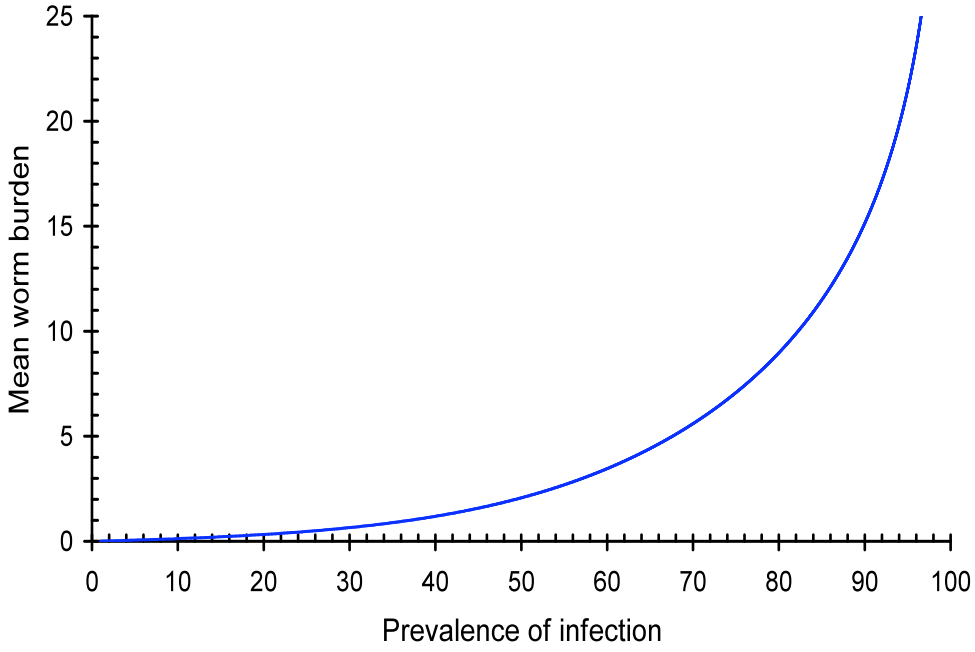

Figure 2 The relationship between the prevalence of infection with an intestinal nematode worm, in this case *Ascaris lumbricoides*, and the mean worm burden estimated by applying the negative binomial distribution using a clumping parameter (*k*) that varies linearly with the mean worm burden (see Guyatt *et al.*, 1990).

The mechanism by which intestinal nematode worms cause disease differs between species: roundworms feed on gut contents, but this probably has only a minor impact on human nutrition as the needs of worms are relatively small; roundworms and hookworms can both cause maldigestion or malabsorption of nutrients; hookworms and whipworms feed on blood and tissue fluids; all species can elicit inflammatory responses that affect appetite and metabolic rate, and they all can cause the diversion of perhaps scarce nutrients to mount responses to infection (reviewed by Hall *et al.*, 2008). By these various mechanisms worms may have effects on haemoglobin concentration and thus on anaemia, on physical fitness and work productivity, and on appetite and growth, both in terms of body weight and height (Alderman *et al.*, 2006; Bhutta *et al.*, 2008; Brooker *et al.*, 2008; de Silva *et al*, 2003b; Gulani *et al.*, 2007;

Guyatt *et al.*, 2001; Hall *et al.*, 2008; Stoltzfus *et al.*, 2004). There may also be indirect benefits through effects on participation in school and intellectual development (Miguel and Kremer, 2004; Bobonis *et al.* 2006).

It is tempting to conclude that simply treating worms will rectify the disease or deficits that they have caused, but this logic is flawed. For example, if worms cause malnutrition and impair children's intellectual development, why would simply removing the worms reverse any deficits? To replace lost haemoglobin or achieve catch-up growth for example, children will need energy, protein and micronutrients (Hall, 2007; Hall *et al.* 2008). And if children have missed school because of illness due to worms, they may need remedial education as well. As children with worms tend to live in poor environments in which undernutrition and intellectual deprivation also occur, removing worms is only a first step in improving child growth, health and development, and additional remedial therapy may be needed.

This suggests that new deworming programmes should not expect immediate improvements in nutritional status and growth unless children are known to consume a diet that is adequate both in quantity and quality. In countries where children already consume a poor diet, dewormed children may require therapeutic micronutrients, supplementary food or even remedial education if they are to recover quickly the losses caused by worm infections. Without them the benefit of deworming may not be readily apparent. The economic analysis of benefits of deworming is best applied to children who can be kept free of moderate or heavy worm burdens throughout their childhood by deworming often enough to prevent moderate to heavy infections from accumulating, ideally supported by sanitation and health education.

As reinfection with intestinal worms can occur immediately after treatment, the aim of deworming is first, to reduce initial worm loads by >80% and thereby eliminate disease, and then to repeat treatment often enough to prevent moderate to heavy loads from being reaccumulated. Periodic deworming also helps to reduce transmission by removing worms, because a female roundworm may produce up to 200,000 eggs a day and has a life-span of up to 18 months. Deworming schoolchildren alone has been shown to reduce transmission to untreated members of the community (Bundy *et al.*, 1992b), so treatment has externalities. However the long term solution is to promote changes in behaviour through public health education so that people use latrines (Nock *et al.*, 2006) and to install effective sanitation to keep people and human faeces apart.

School-age children are most at risk of infection and disease caused by intestinal roundworms and whipworms while hookworms tend to be more common in adolescents and adults (Bundy *et al.*, 1992a). In 2001 the 54th World Health Assembly adopted a resolution to deworm at least 75% of all school-age children at least once a year (WHO, 2001). The global progress made towards meeting this target is reviewed regularly. The most recent data are for 2006, and of the 130 endemic countries, data were available for treatment of school age children in 64, and for preschool children in 51 countries (WHO, 2008). Coverage of preschool children was 55% and of school age children 22%, but only in those countries reporting data.

2 SOLUTIONS

The scientific basis for the short to medium term solution to the problem of intestinal worms – mass deworming – lies in a mixture of epidemiology, pharmacology and economics. First, when the prevalence of infection is greater than 50% the purpose of diagnosis would be to identify uninfected individuals to exclude from treatment rather than to identify those to treat. As Figure 2 shows, the mean worm burden increases exponentially at prevalences above 50% and so therefore does the risk of disease (Guyatt & Bundy, 1991). Because the cost of treatment is much less than the cost of diagnosis; because the drugs to treat worms are very safe, meaning that there is no known harm for an uninfected person to be treated; and because the drugs are effective against all species of intestinal nematode, giving mass treatment (rather than diagnosing and treating people individually) was identified as the simplest and most effective means of treating moderate to heavy infections with intestinal worms (WHO, 1996).

The strategy of mass treatment was made possible by the availability of single dose drugs that treat all main species of intestinal nematode worm (WHO, 1995), although with varying degrees of efficacy:

- Piperazine is an old drug used occasionally at a single dose of 75 mg/kg body weight, but is only effective against roundworms.
- Levamisole given as a single dose of 2.5 mg/kg is effective against roundworms and to some degree against hookworms.
- Pyrantel pamoate given as a dose of 10 mg/kg is effective as a single dose against roundworms and hookworms, but not against whipworms unless given with oxantel (Gustafsson *et al.*, 1987).
- A mixture of pyrantel and oxantel given at a dose of 10 mg/kg is equally effective as mebendazole against roundworms and hookworms, but is more effective against whipworms (Albonico *et al.*, 2002). Oxantel is not currently on the WHO essential drugs list, however.
- A new drug called nitazoxanide is effective against roundworms and whipworms but has to be given twice a day for three days.

The main disadvantage of all these treatments is that body weight needs to be known to determine the dose, which requires a weighing scale. However it is possible that height could be used to estimate the weight of children and from that, the dose of drug, so that the number of tablets can be marked on a "tablet pole". This has been done for ivermectin to treat onchocerciasis and for praziquantel to treat schistosomiasis (Hall *et al.*, 1999).

The most widely used treatments for intestinal nematode worms are two benzimidazole derivatives:

- Albendazole, given as single dose of 400 mg to anyone older than 1 year, is highly effective against roundworms (88% cure rate), effective against hookworm (72% cure rate), but less effective as a single dose against whipworm (28% cure rate) (Keiser and Utzinger, 2008).
- Mebendazole, given as a single dose of 500 mg to anyone older than 1 year, is highly effective against roundworms (95% cure rate) but less effective against hookworm (15% cure rate) and whipworm (36% cure rate) (Keiser and Utzinger, 2008).

An advantage of albendazole and mebendazole is that they are administered as a single, standard dose to anyone older than 2 years, which is simple and ensures compliance. Both are available as flavoured, chewable tablets, which makes them easy to take. There is also some evidence of geographical differences in the efficacy of treatments with benzimidazoles: they seem to be more effective in Africa than Asia (Bennett & Guyatt, 2000).

Studies have shown that albendazole can be given at the same time as praziquantel (Olds *et al.*, 1999), which commonly occurs with intestinal worms in the same children, mainly in sub-Saharan Africa. Co-administration helps to reduce the costs of delivery and treatment (PCD, 1999). It has been assumed that, because mebendazole is very similar to albendaz-ole, praziquantel can also be co-adminstered with mebendazole. The advantage of these single dose treatments is that they ensure compliance with taking the treatment and it means that one person, such as a school teacher, could treat hundreds of children in a day.

Treating children in school is particularly attractive, for several reasons. First, because the prevalence of infection and worm loads tend to be heaviest in children aged 5 to 15 years; because such children contribute most to transmission when they do not use a latrine; and because schools provide an existing infrastructure through which to deliver and administer treatments. In addition, parents are generally very supportive of treating worm infections and appreciate the potential benefits (Brooker *et al.*, 2001). Studies have shown that the financial costs of deworming schoolchildren are modest (discussed in the next section). Generic versions of both mebendazole and albendazole are widely available but there is concern for fake medicines in some parts of the world, so treatments should be tested for active ingredients, or a trial of drug efficacy should be done if the source is not assured.

Although there are costs to distribute treatments to schools, to train teachers and for general administration, it seems generally assumed that teachers do not require any payment in addition to their salary, so that the cost of actually administering treatment is paid for. Whether teachers are willing to take on what could be viewed as a medical responsibility, is another issue, and needs to be dealt with by careful and sensitive training, which will have costs.

In countries in which enrolment rates are low, there is concern that non-enrolled children will miss treatments delivered through schools. The few studies that have been done comparing intestinal worm infections in enrolled and non-enrolled children have not shown significant differences (Beasley *et al.* 2000; Fentiman *et al.*, 2001). Non-enrolled children may actually come from households containing enrolled children (Montresor *et al.*, 2001) so there may be no justification for assuming that there would be differences.

Mass deworming is now being added to programmes supported by UNICEF that deliver capsules of vitamin A to children aged 1 – 5 years, such as Child Health Days (UNICEF/WHO, 2004). A large randomized controlled cluster trial in Uganda of albendazole given every six months to children 1-7 years at Child Health days found significant differences in weight gain between treated children and untreated controls, and the children who got the most doses over the two year study showed the greatest weight gain (Alderman *et al.*, 2006)

The use of albendazole and mebendazole to treat children less than 24 months old was recommended by a WHO informal consultation (WHO, 2003). The rationale is the same as for older children: to treat or prevent disease, mainly because there is concern that the effects of worms may be proportionately greater in small children. Children aged less than 24 months who cannot chew should be given a crushed tablet or syrup, which is typically more expensive than a tablet, both to purchase and to distribute. This is because there is a risk that a child who is unwilling to chew a tablet may choke to death if forced to take one. This happened in Ethiopia in 2007 to four children aged less than 36 months old (WHO, 2007). There are no cost data for the distribution of deworming medication as a syrup to children less than 2 years old.

Ideally all women of reproductive age should be dewormed periodically to prevent the build-up of moderate to heavy infections, especially of hookworm, which can contribute to blood loss and anaemia (Pawlowski *et al.*, 1991). It has recently been estimated that 38 million women of reproductive age in sub-Saharan Africa are infected with hookworms (Brooker *et al.*, 2008). The WHO recommends that albendazole and mebendazole should not be taken by any woman during the first trimester of pregnancy (WHO, 2005). A study in Sierra Leone of treating women with albendazole after the fist trimester found that it helped to prevent a decline in haemoglobin concentration during the second and third trimesters (Torlesse and Hodges, 2000).

More work on the cost-effectiveness of programmes to treat preschool children and pregnant women is required, which will depend on the species of worms, the prevalence of infection, the frequency of treatment per person, and most important, the costs of distributing and giving treatments. As many women in many developing countries do not seek health care until their third trimester of pregnancy, achieving high coverage of women from the start of their second trimester will be an issue. In areas where malaria and hookworm co-occur, treatments for worms could be given to pregnant women in their second or third trimester with, or soon after, presumptive intermittent treatment for malaria.

School-based treatment programmes

The basis for deciding when and how often to give mass treatment is the prevalence of infection with any species of intestinal nematode worm (roundworm, whipworm and hookworm combined) in a survey of schoolchildren in a sample of schools. Any child with any species of intestinal nematode worm is counted as infected; tapeworms and schistosomes are excluded as the drugs used to treat intestinal nematodes do not affect these worms. It is not usually practicable to assess the prevalence of infection in every school, so it is estimated in a representative sample and a decision is made whether to give mass treatment to all children in all schools.

The number of schools to be selected and the method by which they are sampled will depend on the scale of the intended programme of mass treatment. If the programme is to be implemented in an environmentally homogenous area, such as a number of similar districts or a region, then either 10% of primary schools (minimum = 3) up to a maximum of 10 should be selected for study. There are two main ways to select those schools: either with a probability

that is proportionate to the numbers of children enrolled (PPS method), which would tend to select more large, urban or peri-urban schools than small rural schools; or by a lot quality assurance sampling (LQAS) method, which samples schools evenly across a geographic area and is best for health problems that are not evenly distributed. The PPS method is commonly used by UNICEF and other agencies to undertake 30/30 cluster surveys, so will not be described here (Bennett *et al.*, 1991). To select schools using the LQAS method the area should be divided on a map into quadrants of almost equal size, the number depending on how many schools are required, and the school closest to the centre of each quadrant should be selected for study. This method has been used to map the distribution of infections with *Schistosoma* spp (Brooker *et al.*, 2007).

If the area in which a programme is to be implemented is not environmentally homogenous, then it should be divided into ecological zones and the same sampling procedure should be applied to each zone. The findings can then be applied to the administrative units within each zone. If data are wanted by District or Region, then the 10-school survey can be done, but this is unnecessary and wasteful of resources if the districts are environmentally similar.

In each school a sample of fresh faeces should be collected from 40 children, 20 each from two classes containing children who are mostly aged 10 – 14 years. This age group is old enough to understand instructions about collecting their faeces and may be more amenable than classes of older adolescents.

The stool samples should be examined under a microscope for the eggs of intestinal worms, which are characteristic except that the eggs of the two species of hookworms cannot be told apart (WHO, 1994). There are a number of methods to examine faeces, in order of decreasing diagnostic sensitivity: the formalin-ether concentration method; the Kato-Katz smear method; a simple Kato smear; or a simple direct smear of faeces in saline (WHO, 1991). Salt flotation methods are not recommended as they tend to damage hookworm eggs. The Kato methods do not allow the diagnosis of infections with intestinal protozoa at the same time; the other methods do. The first two methods are semi-quantitative and allow an estimate of the concentration of worm eggs in faeces to be made; the other methods are qualitative. The survey to establish the prevalence of worms requires only a qualitative examination of faeces. To allow monitoring for drug resistance a quantitative examination of faeces is needed, but this need only be done in a cohort of children in 10 – 15 schools (400 – 600 children) in the whole country or region in which a programme is implemented.

The mean concentration of eggs in faeces, also called an egg count and expressed as eggs per gram (epg) of faeces, is a rough indicator of the intensity of infection with each species, although there are many reasons why it can be highly variable (Hall, 1982; Engels *et al.*, 1997; Hall & Holland, 2000).

The percentage of children whose faeces contain the eggs of roundworms, whipworms or hookworms should each be determined, as well as the percentage of children who have any of these infections. The species of worms may influence the drug used, as albendazole seems better than mebendazole at treating hookworm (Albonico *et al.*, 1994; Bennett & Guyatt, 2000;

Keiser & Utzinger, 2008) while a high prevalence and intensity of whipworms may need three daily doses to achieve substantial cure rates (Hall & Nahar, 1994; Bennett & Guyatt, 2000) although this is not often done. The combined prevalence is used to determine whether to give mass treatment and how often to treat.

The cost of such surveys depends largely on transport and labour. A vehicle is needed to visit schools to collect faecal samples and return them to a laboratory that has a microscope, unless a portable field microscope is available. A trained technician can examine 30 – 50 samples a day, depending on the method used, which means that the samples from one school can typically be processed in one day. The only materials needed for a direct smear method are non-sterile, reusable bottles to collect and transport faeces, and some reusable glass microscope slides and coverslips. We estimate that the cost per school in 2008 is approximately $87 (40 samples), i.e. $900-$1300 per country (Table 2). If national surveys were done annually, or surveys were done in each Indian state and Chinese province at the same frequency as for a country, annual testing costs would not exceed $0.25m, which is 0.1% of our estimated annual treatment costs (Hall et al 2008).

In 1996 a WHO informal consultation endorsed a WHO recommendation that a combined prevalence of intestinal nematode worms of ≥50% was sufficient to warrant mass treatment of school-age children (WHO, 1996). The aim was to treat disease by eliminating all moderate to heavy worm burdens and to reduce transmission. The WHO also proposed a complicated strategy to decide how often to give mass treatment based on three categories of prevalence and the proportion of moderate to heavy infections based on egg counts for each separate species (WHO, 2002). This required an estimate of the concentration of eggs in faeces which is not easy to do in a small rural hospital laboratory unless the necessary materials are supplied. The biological basis and the practicality of this recommendation was weak.

In 2006 another informal consultation endorsed a reduction in the threshold for mass treatment once a year to 20% in a strategy called "preventive chemotherapy" and simplified the basis for repeating treatments as follows: if ≥50% of children are infected then mass treatment should be given to all school-age children twice a year; if ≥ 20% and < 50% of children are infected then mass treatment should be given to all school-age children once a year (WHO, 2006). Provision was also made for treatment three times a year if the prevalence of infection was ≥50% and resources were available, but no different or higher threshold was specified.

The effect of reducing the threshold for mass treatment from 50% to 20% means that treatments may be given to up to 80% of children who do not need them, which increases the cost per infected person treated by up to fourfold, and increases the cost per diseased person treated by an exponentially greater multiple. This is examined in the next section.

Table 2. Estimated costs of processing stool samples for one school (40 children)

Cost Item	Cost/school/day and basis for cost calculation	Cost/school/day in 2008[3]
Microscopy lab tests	$28 (2001)[1]	$34
Driver	$18 (2000)[2]	$22.50
Operating, car	$14 (2000)[2] (assuming 200 Km/day)	$16.80
Depreciation, car	$10(2000)[2] (assuming life 8 years, 240 days/year)	$12.50
TOTAL		$85.80

[1] Source: Mulligan et al, 2003 (revised 2005). Cost of stool microscopy test $0.67 to $0.70 in South Asia and sub-Saharan Africa, assume 40/day tested

[2] Source: WHO-CHOICE (2008), costs for South Asia and sub-Saharan Africa (based on the three regions SEARO D, AFR D and AFR E)

[3] Source: updated to 2008 using US Consumer Price Index

There are some specific groups who should not be treated. First, as drugs should not be given to women in their first trimester of pregnancy (WHO, 2005) it is recommended that no girl aged 13 years or older should be treated, in case she is pregnant. It cannot be assumed that school-age girls are not sexually active. A study of 9,000 schoolchildren in grades 4 to 6 in primary school in Tanzania found that 20% of girls reported having had sex, but only 39% of 114 girls with biological markers of sexual activity such as an infection, acknowledged having had sex, indicating that such activity was greatly under-reported (Todd *et al.*, 2004). Pregnancy is also a common reason for young girls dropping out of school, particularly in sub-Saharan Africa.

Second, children who are sick for any reason when treatments are scheduled to be given should not be treated. This is not because treatment is dangerous, but because if a sick child subsequently dies the treatment could be mistakenly associated with the death which could endanger the programme. When very large numbers of children are being treated on the same day the probability that a child will die is no longer very small.

It is good practice to monitor the efficacy of treatments with anthelmintic drugs so that the development of drug resistance can be detected (WHO, 1999). This is done by examining faecal samples collected from a sample of the same individuals before and after treatment and then calculating the proportion of previously infected people whose faeces no longer contain worm eggs. This is called the cure rate and can be calculated for each species.

A more sensitive measure of efficacy is the egg reduction rate (Bundy *et al.*, 1992a). This is the average difference in the concentration of eggs of each species before and after treatment expressed as a percentage of the initial average egg count. However, if the fecundity of worms is influenced by the number of worms present in the gut (Hall and Holland, 2000) then the fecundity of worms left in the gut after incomplete treatment may increase proportionally after treatment so that the efficacy of treatment measured as an egg reduction rate may be underestimated (Kotze and Kopp, 2008).

The risk of developing drug resistance can be minimised by ensuring that a very high cure rate is achieved, but this is difficult to do for whipworms without giving multiple doses of albendazole or mebendazole (de Silva *et al*, 1997; Bennett & Guyatt, 2000). Repeated treatment of any residual worm load with the same drug could lead to the selection of worms that are resistant to the treatment.

When repeated treatments are given as a part of disease control programmes it is best if two drugs with different mechanisms of action are alternated or coadministered, as the WHO now recommends to treat malaria, for example. This is based on the low probability that resistance will develop in the same species to two drugs at the same time and that, if there is resistance to either drug, at least one will be an effective treatment. Current programmes to treat intestinal worms rely heavily on albendazole and mebendazole, which are closely related treatments with the same mode of action, so there is a risk that resistance will develop if these drugs are used widely and repeatedly. Resistance to these drugs is common among the intestinal worms of farm animals as the drugs have been widely and heavily used and because sheep and cows often continue to feed on pastures that may be heavily contaminated with the eggs of resistant strains of worms from themselves or other animals.

The authors' recommendation is that operations research should be undertaken to examine the effect on resistance in intestinal nematode worms of alternating albendazole or mebendazole treatment for several years with a combination of pyrantel and oxantel. This combination is available in Indonesia, Malaysia, Singapore, the Philippines and Venezuela. If this proved effective, pyrantel/oxantel would need to be added to the WHO Essential Medicines list, and it is likely that increased demand would lead to inexpensive supplies of pyrantel/oxantel being sourced internationally.

3 ECONOMIC ANALYSIS

The cost of deworming can be looked at in three ways: as the cost per person treated, as the cost per infected person treated, and as the cost per diseased person treated. When the prevalence of infection approaches 100%, as it can in places where transmission is very intense, then the cost per infected person treated approaches the cost per person treated. However when the prevalence is <100% some uninfected people will be treated unnecessarily, so the cost per infected person rises. This is shown in Table 1 (from Hall *et al.* , 2008) for prevalences of infection between 90% and 20%; the lower value is the threshold at which mass treatment is recommended by the WHO (2006). When the prevalence is as low as 20%, the cost of drugs per infected person treated is 5 times the cost per person treated.

The cost per diseased person treated depends on the prevalence of infection (p), the mean worm burden (M) and the clumping parameter k of the negative binomial distribution in which $p = 1 - (1+M/k)^{-k}$. Values of k for intestinal nematode worms are typically < 1, which means that worms are highly aggregated such that a small proportion of individuals have moderate to heavy infections and are likely to be diseased. The negative binomial distribution can be used to estimate values for the prevalence of infection and k for any mean worm burden, assuming

that *k* varies linearly with M (Guyatt *et al.*, 1990), and to estimate the proportion of individuals that have more than any given threshold of worms.

Table 1 shows that when the prevalence is 20% then only 0.01% of individuals will have ≥10 worms, a relatively low threshold at which disease might occur so that, if mass treatment was given, it would cost USD 486 per diseased person treated. (For a threshold of ≥15 worms the cost is about USD 27,000 per diseased person treated and for a threshold of ≥20 worms, USD 1.4 million per diseased person treated.)

The analysis presented in Table 1 is based on data for a single species of worm, *Ascaris lumbricoides*. Because the distribution of disease for any species is driven largely by the extent to which worms are aggregated in a few hosts, the clumping parameter *k* is of great importance. As values of *k* range from 0.03 – 0.6 for hookworms and from 0.2 – 0.4 for whipworms (Anderson & May, 1991), they indicate a greater degree of aggregation of these species than for roundworms, for which values of *k* range from 0.3 – 0.9 (Anderson & May, 2001). Similarly the coefficients in the equation linking *k* and M (the worm burden) in Table 1 have been estimated for roundworm, but are not known so well for the other species. Hence the numerical values in the table are not necessarily a perfect guide to cases of infection with whipworm or hookworm, or indeed mixed infections with more than one kind of intestinal worm. However the main point, that disease is highly aggregated, especially at low prevalences of infection, is likely to hold true.

The analysis presented in Table 1 is also dependent on the threshold used to classify any individual as diseased or not, something that is not known, mainly because the effects of worms are hard to quantify in the first place and vary between species. For example, assuming an equal sex ratio, 10 roundworms weigh about 25 g, 15 worms weigh 35 g and 20 worms weigh about 45 g, which is about 0.3% of the body weight of an underweight 6-year old school girl of 15 kg (WHO, 1983). For the hookworm species *Ancylostoma duodenale*, 10 worms are estimated to cause a blood loss of 2 ml/day, 15 worms 3 ml/day and 20 worms 4 ml/day; the same figures for the other hookworm species, *Necator americanus*, are 0.4, 0.6 and 0.8 ml/day of blood a day, as the two species differ in the volume of blood loss that they cause (Roche and Layrisse, 1966). Both species now co-occur widely throughout the world. The loss of blood caused by the same number of whipworms is estimated to be 0.05, 0.07 and 0.1 ml/day of blood (Layrisse *et al.*, 1967) although the inflammatory response to the head of the worms embedded in tissues may be more important.

These differences highlight that we do not know how to quantify disease due to a single worm species, let alone concurrent infections of two of more species, so the threshold number of worms used to define disease in preschool children or schoolchildren, whether malnourished or not, is arbitrary. But whatever the threshold, the risk of having more than say, 10 worms, becomes extremely small when the prevalence is lower than 50%, so that few individuals will benefit.

Table 1 suggests that when the WHO threshold of 20% prevalence is applied to give mass treatment, then only 1 in every 10,000 people treated will have 10 or more worms. We think

that this prevalence threshold is too low to be a cost-effective way of treating disease cause by worms.

We propose the following thresholds and frequencies of treatment based on the combined prevalence of infections with roundworm, hookworm and whipworm in schoolchildren (Hall *et al.*, 2008):

- if prevalence is <40%, treat only moderately or severely underweight, wasted or anaemic children or children with diagnosed infections;
- if prevalence is 40 – <60% , give mass treatment once a year, checking every 2 y to see if prevalence is <40%;
- if prevalence is 60 – <80%, give mass treatment twice a year, checking after 2 y that prevalence is 40 - <60% then give annual mass treatments;
- if prevalence is 80 – 100%, give mass treatment three times a year, checking after 2 y, so that if prevalence is 60 – <80% treat twice a year and if 40 - <60% then treat once a year.

In addition schools should be supported to install and maintain sanitary latrines, separately for boys and girls; provide clean water and soap to wash hands; and to promote healthy behaviours through health education.

The costs and cost-effectiveness of treating children aged 2 to 14 based on the two sets of thresholds have been estimated for 103 countries plus India and China at the subnational levels of states and provinces respectively, because of their large size (Hall *et al.,* 2008). (The countries in Asia which were formerly members of the Soviet Union were excluded, as prevalence data were not available). The analysis found that the WHO thresholds imply higher annual treatment costs ($276 million annually compared to $224 million for the proposed new thresholds), and imply a smaller proportion of expenditures going to children who are infected (61% as compared to 73%), and a smaller proportion of expenditures going to children with 10 or more worms (21% as compared to 31%) (Hall *et al.*, 2008).

There have been several analyses of the costs and cost-effectiveness of deworming delivered through schools and to preschool children during Child Health Days. Miguel and Kremer (2004) examined a programme in which Kenyan schoolchildren were treated twice a year with albendazole in schools in which the prevalence with intestinal nematode worms was >50% and annually with praziquantel in schools in which the prevalence of schistosomiasis was >30%. The costs of the programme were based on a prior estimate of USD 0.49 per year per child (PCD, 1999). It was estimated that deworming decreased absenteeism by 25% and was claimed to be a more cost-effective way of increasing school participation than any alternative, including school subsidies (Miguel & Kremer, 2004). It can be estimated from these figures (Horton *et al.* 2008) that the present value of increased wages associated with increased school achievement gives a benefit:cost ratio of 60:1, which would fall if it was necessary to hire additional teachers because of increased attendance, but is still over 3:1. There were also external effects on untreated children in participating schools, probably due to reduced transmission of intestinal nematode worms, and there were external effects on children in non-participating schools,

probably through effects on the transmission of schistosomiasis, although the latter relied on non-experimental methods of estimation (Miguel & Kremer, 2004).

Table 1. Estimates of the drug costs per person treated once for infections with *Ascaris lumbricoides* using a drug costing USD 0.03 per dose.

As there is a linear relationship between the mean worm burden (M) and the clumping parameter *k* for *A.lumbricoides* (Guyatt and Bundy, 1991), this relationship[a] has been used to estimate values of *k* for mean worm burdens in steps of roughly M/2, starting at M=30, with the aim of giving proportions infected (*p*) from 20 – 95% using the equation for the negative binomial distribution, in which $p = 1-(1+M/k)^{-k}$. The negative binomial function (*pnbinom*) of the R programme (R Development Core Team, 2007) was then used to estimate from values of *k* and M the proportion of people having more than 10, 15 or 20 worms, arbitrary thresholds that could be used to classify a worm burden as moderate or greater. The costs were then estimated per person, per infected person based on *p*, and per diseased person treated based on the proportions infected with ≥10, ≥15 or ≥20 *A.lumbricoides*. Some values were < 0.0001.

Proportion Infected (*p*)	Mean Burden (M)	Clumping parameter (*k*)[a]	Proportion infected With			Costs in USD per				
			≥10 worms	≥15 worms	≥20 worms	Person	Infected Person	Diseased person ≥10 worms	Diseased person ≥15 worms	Diseased person ≥20 worms
0.95	30.0	0.850	0.6860	0.5817	0.4956	0.03	0.03	0.04	0.05	0.06
0.90	20.0	0.678	0.5430	0.4322	0.3483	0.03	0.04	0.06	0.07	0.09
0.85	14.6	0.585	0.4400	0.3316	0.2545	0.03	0.04	0.07	0.09	0.12
0.80	11.0	0.523	0.3563	0.2539	0.1852	0.03	0.04	0.08	0.12	0.16
0.70	6.4	0.444	0.2222	0.1381	0.0886	0.03	0.04	0.14	0.22	0.34
0.60	3.6	0.396	0.1159	0.0580	0.0302	0.03	0.05	0.26	0.52	0.99
0.50	2.0	0.368	0.0460	0.0162	0.0060	0.03	0.06	0.65	1.85	5.01
0.40	1.2	0.354	0.0149	0.0033	0.0008	0.03	0.07	2.01	9.09	38.88
0.30	0.6	0.345	0.0016	0.0001	0.0000	0.03	0.10	18.80	230.81	2,658.33
0.20	0.3	0.339	0.0001	0.0000	0.0000	0.03	0.15	485.68	27,335.62	1,435,480.19

[a] $k = a + bM$ in which a = 0.334 and b = 0.0172 (Guyatt and Bundy 1991)
Source: Hall, et al (2008)

In a school based deworming programme in Uganda Brooker *et al.* (2008) estimated that the cost of drugs was USD 0.22 per child treated per year for three years of which albendazole cost 10%, praziquantel cost 82% and the remainder was the cost of shipping to Kampala. As generic drugs were used the cost was less than a third of similar programmes in Ghana and Tanzania, which used proprietary drugs (PCD, 1999). The total cost per child treated was USD 0.54 per year, so that the drugs were 40% of the overall cost, which confirms that school-based programmes are a relatively efficient way to administer some types of health interventions. However the costs per child varied between districts from USD 0.41 to USD 0.91 and were lowest in districts with the highest population density, mainly because fixed costs such as allowances for district officials were spread over larger numbers of children treated. There was

a 52.5% reduction in the proportion of anaemia cases in a cohort of children over 3 years of monitoring, from 35.2% to 18.5%, but there was no control group. Thus the true effect of treatment could not be separated from natural increases in haemoglobin concentration with age among boys, from the effects of the diet on iron and vitamin intake, and perhaps changes in malaria transmission over the 3 year period as a result of control programmes. The cost-effectiveness per case of anaemia prevented was estimated to be USD 3.19, which also varied by district, ranging from USD 1.70 to USD 9.51, but costs were probably larger because the change in the prevalence of anaemia was over-estimated. The effectiveness of the programme also depended on epidemiological differences as the most cost-effective district had the highest initial prevalence of anaemia, but also varied with other unexplained factors.

The cost-effectiveness of the school-based programme in Uganda compares with USD 7.43 in mainland Tanzania (Guyatt *et al.*, 2001) and USD 3.57 in Zanzibar, Tanzania (Stoltzfus *et al.*, 1998). Other factors also contributed to the differences in cost, such as the frequency of treatment and the period over which outcome measurements were made.

If we summarize the data for schoolchildren, the cost per child per round of treatment is approximately $0.15, assuming that deworming costs are shared with another program, such as schistosomiasis treatment.

Two studies provide estimates of costs, but not cost-effectiveness, of deworming preschool children. Alderman *et al.* (2006) found a statistically significant effect of 6-monthly treatment with albendazole given at Child Health Days in Uganda on weight gain of children < 7 y age. A single dose of proprietary albendazole was estimated to add USD 0.21 per child to the cost of a child health day because a proprietary brand of albendazole was used for scientific reasons, but all the costs of staff were attributed to giving vitamin A and other activities. The annual cost for bi-annual Health Days was USD 0.42. Substituting generic drugs could reduce the cost considerably, however it is not reasonable to attribute all the staff costs to the other activities.

Fiedler and Chuko (2008) estimated the cost of distributing albendazole in Ethiopia twice per year during Child Health Days at USD 0.56 per child per round of treatment, and prorated staff costs among the various activities: deworming, giving vitamin A, and nutrition screening. Thus the cost per child to deworm preschool children is about $0.25 per child per round, as long as it can be combined with an existing health intervention such as Child Health Days or can be incorporated within the primary health care system, if coverage is good.

Bobonis *et al.* (2006) analyzed the cost of providing deworming and iron supplements in Indian preschools. Children aged 2 - 6 years in preschools in poor communities in eastern Delhi were given albendazole and iron supplements providing 33.3 mg of elemental iron with folic acid for three consecutive days, both administered three times per year at a "health camp". Additionally, all children received 200,000 IU vitamin A once a year as did all children in two otherwise untreated control groups. Only 30% of children were infected with worms. There were significant differences between groups in the gain in z-scores of weight-for-age and weight-for-height, but the treated group had significantly lower mean values at baseline (Bobonis *et al.*, 2006). There was no significant change in haemoglobin concentration but

participation rates in preschool increased by almost 6% thereby reducing absenteeism by 20%. The cost was estimated at USD 1.70 per child per year. Although no formal cost-effectiveness analysis was undertaken as the effects of iron and deworming cannot be separated, it confirms generally the findings of Miguel and Kremer (2004). There are no cost-effectiveness studies in preschool children, to our knowledge. We can make estimates of the order of magnitude of the effect of deworming in preschoolers, as follows. The most significant outcome of deworming from an economic perspective is the reduction or prevention of anaemia, assuming that the diet of anaemic treated people contains sufficient nutrients to enable haemopoiesis; the effect on growth is important for health but not large enough to have a significant economic impact. According to Bhutta *et al.* (2008) the size of the reduction in anaemia due to deworming children ranges from 4.4% to 21%, with a median value of 13%, which translates to an increase in haemoglobin of 1.71 (0.70-2.73) g/L.

Horton and Ross (2003, corrected 2006) estimated for a range of developing countries that the present value of the median cognitive loss attributable to anaemia is USD 15-25 per child. Hence reducing anaemia by 13% could lead to benefits of approximately USD 2.60 per preschool child compared with a cost of deworming of USD 0.40-50 per child. Thus, the benefit:cost ratio is 5:1 to 6:1 in this age-group, but would be reduced to 2.4:1 if a 5% discount rate were used. These estimates are conservative and do not take into account benefits due improvements in weight and height. The benefit:cost ratio is likely also to vary with the coverage of treatment given to the target group.

But if the potential improvement in haemoglobin concentration after deworming is constrained by a deficiency of any nutrient or by another cause of anaemia, such as malaria, then the magnitude of the potential impact of deworming will be underestimated. A study in Tanzania of giving iron and vitamin A to schoolchildren after treating hookworms and schistosomiasis with albendazole and praziquantel showed an absolute increase in haemoglobin concentration of 22.1 g/L and relative increase of 18.5 g/L (95% CI 14.8 – 22.2) compared with an increase in controls, who were only dewormed, of 3.5 g/L (Mwanri *et al.*, 2000). This small increase in the haemoglobin concentration of controls is similar to the effect estimated by Bhutta *et al.* (2008). For this reason children should be given a course of micronutrients supplements that provide vitamin A, folate, vitamin B_{12} and iron, after deworming. Teachers in Mali and the Philippines have been shown to be able to give weekly iron tablets to their pupils with statistically significant effects on haemoglobin concentration (Hall *et al.*, 2002; Roschnik *et al.*, 2004). The costs have not been estimated but a multivitamin supplement for adults costs USD 0.01 per tablet if bought in large quantities in a country such as Bangladesh.

It is reasonable to use a cost of about USD 0.50 per preschool child treated per year (two rounds of treatment), and about USD 0.30 per school-age child treated (two rounds of treatment), for up to 80% of the target population, but this assumes that generic not proprietary drugs are used and that deworming is combined with another intervention for preschool children or is given in schools, thus reducing the distribution and delivery costs. Distributing treatments in Child Health Days is likely to be more efficient in large communities than small ones, but is less likely to reach remote areas, although such areas are also likely to be less densely populated. The implication is that the costs of increasing coverage are likely to increase as coverage also

increases. The coverage of school-age children will depend on enrolment rates, which are improving as a result of efforts to achieve a Millennium Development Goal. But there is no reason why coverage of children who are enrolled and attending school should not approach 100%, especially if children who are absent from school are treated later.

We have undertaken elsewhere detailed calculations of the annual treatment costs of deworming, including both drug and delivery costs (Hall *et al.*., 2008). For 100% coverage of all children in 105 developing countries, the costs are $224 million per year using the proposed (more cost-effective) treatment thresholds, or $276 million per year using the current WHO thresholds. Although this is a large annual expenditure, the potential benefits in terms of improved child health and education are very large, using the benefit:cost ratio of 6:1 (preschoolers) and even higher for school-age children.

4 Conclusions

This paper has discussed a number of policy recommendations. We have focussed only on intestinal nematodes and excluded schistosomiasis and other worms. Mass deworming of schoolchildren is inexpensive and safe, with the only caveat that care is needed when treating adolescent girls over the age of 12y to be sure they are not in the first trimester of pregnancy. Mass deworming of preschoolers aged two and above is also inexpensive and safe. Operational cost data are lacking for deworming preschoolers under the age of two, although deworming is also safe for this group using syrups. Operational cost data are also lacking for pregnant women.

Studies and models suggest that mass deworming is cost-effective when the prevalence of infection with intestinal nematodes exceeds 50%, as first recommended by the WHO (1996). The WHO (2006) recommendation also allow for treatment three times per year where infection is severe. Cost-effectiveness data however do not support the "preventive chemotherapy" approach of treating once per year for prevalence rates as low as 20%, without further evidence. Our recommendation is that the thresholds 40%, 60% and 80% offer a simple basis on which to give mass treatment 1x, 2x or 3x a year, and cover the increasing risk of disease while minimizing costs.

Albendazole and mebendazole are both effective and low-cost and have the advantage that they can be co-administered with praziquantel in places where individuals are infected both with intestinal worms and schistosomiasis. However, given concerns about the development of drug resistance, it would be best to alternate them with a drug that has a different mechanism of effect. It is recommended that operations research be conducted alternating albendazole/mebendazole with a combination of pyrantel and oxantel; the dose of the latter could be estimated based on height, to avoid the need for weighing scales or a standard dose for age could be determined. This could lower the risk of developing drug resistance to albendazole and mebendazole, neither of which is fully efficacious against hookworms or whipworms.

A survey of the prevalence of worms in a sample of schools is recommended to determine if treatment is warranted and how often it should be given. Faecal egg counts should be estimated in children in a sample of schools to estimate the cure rate and the egg reduction rate to monitor drug effectiveness and detect drug resistance. Although such surveys increase costs (by approximately 0.1% worldwide), they can increase cost-effectiveness by avoiding unwarranted treatments.

The costs of treatment are not insubstantial; although the cost per school-age child is only about USD 0.30 per year for two rounds of treatment (including distribution costs) (and $0.50 per year per preschool child), the annual global costs would be $224 million (proposed new thresholds) or $276 million (WHO thresholds). However, the benefits in terms of improved health, nutrition and education are also very substantial, given the very high benefit:cost ratio of intervention.

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The Copenhagen Consensus Center is headed by Bjørn Lomborg

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