Can we deworm this wormy world?

D A P Bundy and N R de Silva

WHO Collaborating Centre for the Epidemiology of Intestinal Parasitic Infections, Wellcome Trust Centre for the Epidemiology of Infectious Disease, University of Oxford, Oxford, UK
(*Present address: Department of Parasitology, Faculty of Medicine, University of Kelaniya, Ragama, Sri Lanka)

While programmes such as the Rockefeller campaign were specifically targeted at a particular parasite species, the current trend is towards the simultaneous control of all the major geohelminth species. New, broad-spectrum, low-cost anthelmintics and new understanding of epidemiology have led to more cost-effective and sustainable strategies. The WHO, UNICEF and the World Bank all now support global and regional efforts to achieve control of morbidity from intestinal worms. In this paper, we aim to show what's new in clinical helminthology and what has brought about the great improvement in the success of the new approaches to control.

People have always had worms. There is evidence for infection in Pre-Columbian Incas and Pharaonic officials of the Middle Kingdom. Intestinal nematode infection was historically common in Northern Europe: in Scandinavian Vikings, in Imperial Romans, and in the mediaeval vicars chorale at York Minster. Fifty years ago this year, a classical paper entitled This Wormy World showed that intestinal nematode infections were amongst the most common of human infections. Today, these infections still affect more than a quarter of the world's population.

Their ubiquity has stimulated several major control programmes conducted on a scale only exceeded by global vaccination programmes. The Rockefeller hookworm eradication campaign was started in the southern US at the turn of this century, extended globally in 1913, and finally terminated in the 1950s. Like many early programmes, it was unable to achieve its stated objective, the eradication of hookworm infection and disease with the tools then available. In more recent times, however, several countries, notably Israel, Japan and South Korea have achieved sustained and successful control of intestinal nematode infections. The Japanese national programme in particular has been remarkably successful: the nation-wide overall prevalence of intestinal nematodes was reduced from 73% in 1949 to < 1% in 1990.
What’s new in understanding helminth epidemiology?

The epidemiology of helminth infections is fundamentally different from that of all other infectious agents. The key to this difference is helminth reproductive behaviour: while most species reproduce within the definitive host in the sense of producing stages which are infective to other hosts, only a very small minority of helminth species (e.g. *Strongyloides* and *Capillaria* spp.) multiply within the same host individual. Thus, each worm that establishes in a host is the result of a separate infection event, and the number of infectious stages shed (the infectiousness of the host) is a function of the number of worms present. The size of the worm burden (the intensity of infection) is, therefore, the central determinant of helminth transmission dynamics, and is also the major determinant of morbidity, since the occurrence of disease is related to the intensity of infection, usually in a non-linear fashion.

Worm burden and infection

Worm burdens are neither uniformly nor randomly distributed amongst individuals, but are highly overdispersed, such that most individuals have few worms while a few hosts harbour disproportionately large worm burdens. This pattern has been described for *Ascaris lumbricoides* (roundworm), both species of hookworm, *Trichuris trichiura* (whipworm) and *Enterobius vermicularis* (pinworm). Most studies suggest that approximately 70% of the worm population is harboured by 15% of the host population. These few heavily infected individuals are simultaneously at highest risk of disease, and the major source of environmental contamination.

Studies of re-infection with all the major geohelminths and *E. vermicularis* have shown that individuals are predisposed to a high or low intensity of infection; the size of the worm burden re-acquired after successful treatment is positively associated with the intensity of infection before treatment. Longitudinal studies of *T. trichiura* and *A. lumbricoides* have confirmed that this positive association reflects a direct relation between the rate of re-infection and initial infection status. Thus, in an endemic community, there is a consistent trend for an individual to have an above (or below) average intensity of infection. This trend is more apparent in children with *A. lumbricoides* and *T. trichiura* infection, and more apparent in adults with hookworm and *E. vermicularis* infections, perhaps reflecting the different age-intensity patterns of these species.

This pattern is also apparent at the family level. In endemic areas, more families tend to have a majority of family members with heavy (or
Can we deworm this wormy world?

light) infections with T. trichiura and A. lumbricoides than would be expected by chance, whereas families with a mixture of both heavily and lightly infected individuals are less common than would be predicted; heavily infected individuals tend to be aggregated in families. Studies of these parasites in Mexico and Malaysia indicate that families also exhibit predisposition to infection. Strongyloides stercoralis infections have also been shown to be aggregated by household in endemic foci in Bangladesh and Jamaica. In both studies, the spatial distribution of cases was suggestive of close contact, person-to-person transmission, which has not been shown previously for a geohelminth.

**Age and infection**

The age-dependent pattern of infection prevalence is similar amongst the major intestinal helminths, exhibiting a rise in childhood to a relatively stable asymptote in adulthood. Maximum prevalence is usually attained before 5 years of age with A. lumbricoides and T. trichiura, and in young adults with hookworm infections. The two species of Strongyloides infecting humans exhibit age-prevalence patterns which are quite different from each other and unique among nematodes infecting humans. S. stercoralis is typically rare in children and studies from endemic foci in Japan and Poland indicate that the majority of infections occur in people over 40 years of age. In contrast, the S. fulleborni-like parasite in Papua New Guinea is most prevalent in children under 5 years of age.

Although the general pattern of the age-prevalence of hookworm infection indicates that infections are acquired gradually and do not peak until young adulthood, compelling circumstantial evidence from China indicates that Ancylostoma duodenale can pass from the mother to her neonate to cause ‘infantile hookworm disease’, a condition characterized by diarrhoea with tarry stools, anorexia and vomiting, followed by severe anaemia. It is often fatal if left untreated. It has been suggested that infection can occur following the use of sand-stuffed diapers containing contaminated soil, or through transmammary transmission of larvae.

Prevalence data indicate the proportion of individuals infected, but do not provide a simple indication of the number of worms harboured. The marked non-linearity of the relationship between prevalence and intensity is a direct statistical consequence of the overdispersed pattern of intensity. For most helminth species, the initial rise in intensity with age closely mirrors that of prevalence but occurs at a slightly slower rate. For A. lumbricoides and T. trichiura, maximum worm burdens occur in human populations at 5–10 years of age, and for hookworms at 20–25 years. The most important differences in the age-intensity profiles of
these species become apparent after peak intensity has been attained. A. lumbricoides and T. trichiura exhibit a marked decline in intensity to a low level which then persists throughout adulthood, whereas in hookworm infections, the intensity attains a stable asymptote or rises marginally in adulthood. Thus, in A. lumbricoides and T. trichiura, a similar proportion of children and adults are infected, but the adults have substantially smaller worm burdens. With hookworm infections, in contrast, more adults are infected and they have larger worm burdens.

Thus current understanding of epidemiology suggests that reducing intensity rather than prevalence should be the major aim of control. And that although there is a great deal of heterogeneity in intensity patterns, for some of the most common helminths the most intense infections are found in children, particularly school children, while some other infections are important in adults, particularly mothers.

What's new in understanding impact on health?

There are two main areas in which our understanding of the impact of intestinal nematode infections on the health of humans has advanced in recent years. Firstly, it is becoming increasingly clear that the effects of infection are worse than they were assumed to be in the past. Secondly, there is increasing evidence that chemotherapy (i.e. treatment of the infection) can reverse most of these effects.

Morbidity and infection

Hookworms have long been recognised as an important cause of iron-deficiency anaemia. The feeding behaviour of hookworms results in mechanical blood loss into the gut and the per capita loss of blood is constant. Despite this, the severity of the resultant iron-deficiency anaemia is not linearly related to the worm burden, as it is governed by many other factors, including the iron status and general nutritional status of the host, the quality and quantity of iron sources in the diet, the absorptive properties in the gut, ulcers, gut lesions, and other infections which may adversely influence iron status. Since the largest worm burdens in hookworm infections are generally seen in adults, hookworm-related anaemia was seen principally as a problem of the older population, especially adolescent girls and women of child-bearing age. However, there is now evidence from intervention studies in Zanzibar and Tanzania, that hookworm infections also contribute significantly to anaemia in schoolchildren.
In contrast to hookworm, *A. lumbricoides* and *T. trichiura* were widely held to cause little ill-health in the host, except for the rare infections which led to serious complications such as intestinal obstruction (in ascariasis) or rectal prolapse (in trichuriasis), complications generally associated with a very heavy worm burden. However, intervention studies have shown that infection with as few as 10–15 *A. lumbricoides* is associated with reversible deficits in growth and physical fitness in school age children\textsuperscript{17-19}. Similarly, *T. trichiura* has been recognised as causing trichuris dysentery syndrome in heavily infected children, and growth retardation and anaemia in children with less heavy infections\textsuperscript{20}. Fortunately, it appears that many of the growth and nutritional deficits caused by these helminth infections are reversible with the use of anthelmintics; in fact many of the studies that provide the clearest causative evidence for health deficits in intestinal nematode infections are intervention studies. For example, children with trichuris dysentery syndrome have been shown to exhibit ‘catch-up growth’ after treatment of intense infections with *T. trichiura*\textsuperscript{21}. In addition, a recent study in northern India has shown that albendazole given every 6 months to children aged 1–4 years led to an extra weight gain of 1 kg over a period of 2 years, a 35% difference\textsuperscript{22}. The global burden of disease attributable to the major geohelminths has been estimated using the disability adjusted life year (DALY) metric\textsuperscript{23,24}. These estimates indicate that intestinal nematodes are a leading contributor to the burden of disease in school children.

**Cognition and infection**

There is increasing evidence that intestinal helminth infections can have a detrimental effect on cognition and educational achievement in children\textsuperscript{25}. Many of the sequelae of helminth infection such as undernutrition, and iron deficiency anaemia, are associated with deficits in cognitive functioning\textsuperscript{26,27}. Low weight for age (stunting) has been associated with detriments in cognitive function, in mental development, in behaviour and in educational achievement; it is a striking feature of intense trichuriasis\textsuperscript{20} and a not uncommon consequence of ascariasis\textsuperscript{19}. Early studies provided correlational evidence that children infected with hookworm, and to a lesser extent, *A. lumbricoides*, suffered detrimental effects on educational achievement but did not separate the effects of infection from those of confounding variables such as socioeconomic status\textsuperscript{23}. The possibility of a causal association between helminth infection and education or cognitive function has been addressed by a few intervention studies. The effect of trichuris dysentery syndrome on the mental development of Jamaican schoolchildren was
examined in a case-controlled study. Significant improvement was seen after one year, in nutritional status and in the locomotor subscale of the Griffiths test of mental development. In a double-blind placebo controlled trial involving children with moderate-heavy loads of *T. trichiura*, expulsion of worms led to a significant improvement in tests of auditory short-term memory and a highly significant improvement in the scanning and retrieval of long-term memory.

Thus the implied evidence for an effect of helminth infection on cognitive function is persuasive, but the evidence from correlational and intervention studies still leaves many uncertainties concerning the extent and nature of the effect. Even small effects will have major practical implications for child development, since the peak of infection intensity, and presumably impact on cognitive ability coincides with the age when children are in school. For most children in low income countries, this will be their only opportunity for formal education, and the opportunity may be compromised by ill-health.

**Mortality and infection**

Geohelminth infections rarely cause death. However, because the global number of infections is so large, even rare events could be of some significance. The WHO attributes 65 000 deaths a year to hookworm infections, 60 000 deaths a year to *A. lumbricoides*, and 10 000 deaths a year to trichuriasis; the means by which these estimates are derived are not described. Using a mathematical model and whatever little empirical data are available, it has been estimated that the acute complications of *A. lumbricoides* infections (mainly intestinal obstruction and biliary complications) could result in approximately 10 000 deaths each year, mostly affecting children below the age of 10 years. *T. trichiura* may cause a similar number of deaths through trichuris dysentery syndrome or intussusception and hookworm probably contributes to a larger number of deaths than do ascariasis and trichuriasis, but there is a general lack of empirical data. It is safe to conclude, however, that the burden of ill health attributable to geohelminths is related less to mortality than to the insidious effects on physical and mental growth.

**What’s new in treatment?**

The drugs now available to treat the major geohelminth infections are simple to use, safe, effective, relatively inexpensive and have a broad spectrum of activity. Albendazole and mebendazole are the most effective drugs against ascariasis, trichuriasis, enterobiasis and hookworm infections. They are recommended for use by the WHO for anyone older
than 1 year, as a single standard dose. The single doses recommended by the WHO of 400 mg albendazole or 500 mg mebendazole may not achieve a complete cure, especially with heavy infections of whipworm or hookworm, but they have been shown to reduce worm burdens significantly, and thus reduce the risk of morbidity. The use of either albendazole and mebendazole for the treatment of intestinal nematode infections is associated with very few side effects; the cost of drugs ranges from US$ 0.02 to US$ 0.2 per dose. An analysis of the costs of providing annual treatment to school children in Ghana and Tanzania has shown that the costs of school-based delivery are so low that even if two drugs are given (albendazole or mebendazole for intestinal worms, and praziquantel for the schistosomes), the cost can be less than US$ 1.00 per child treated. These considerations have led to the recommendation that mass anthelmintic treatment targeted at schoolchildren should be carried out without prior individual screening where surveys of school-age children indicate that the prevalence of intestinal helminths exceeds 50%.

The treatment of hookworm infections in pregnancy is an important issue, since pregnant women are at a particularly high risk of developing iron-deficiency anaemia, especially in areas where nutritional anaemia is endemic. Mebendazole and albendazole are teratogenic in rats. The WHO at present recommends that mebendazole and albendazole should not be used in the first trimester of pregnancy, although high priority should be accorded to the treatment of pregnant women.

The chemotherapy of strongyloidiasis, which was largely based on the use of thiabendazole, has been long hampered by low cure rates and high frequency of unpleasant side effects, leading to poor patient compliance. However, recent studies have indicated that both albendazole and ivermectin are of value in the treatment of this infection. Albendazole, like thiabendazole, has to be administered for at least 3 days but, although the cure rates are lower (38–95%, depending on the dose schedule and the follow-up period) than with thiabendazole, the mild nature of the side effects leads to better patient compliance. Ivermectin, in a single dose of 150–200 mg/kg, also appears to provide a good alternative, with high cure rates (85–100%) and mild side effects, even in immuno-compromised patients. Multiple dose ivermectin was found to be effective in curing strongyloidiasis in a small group of HIV-positive patients with Strongyloides hyperinfections, a condition which is often fatal.

**Drug resistance to anthelmintics**

As yet there are no confirmed reports of anthelmintic drug resistance in a soil-transmitted helminth infection in humans. However, resistance to benzimidazoles and levamisole, as well as to avermectins to a lesser
Tropical medicine: achievements and prospects

extent, are commonly reported in the veterinary literature\textsuperscript{33}. Thus there is understandable concern that this problem may threaten the use of antihelmintic drugs for the control of soil-transmitted nematodes in humans.

What's new in community control?

Although helminths can infect all members of a population, it is clear that there are specific groups who are at greater risk of heavy infection than others, and that some are more vulnerable than others to the harmful effects of chronic infections. They are: school age children; preschool children, especially those nearing school age; and women of child-bearing age, including adolescent girls. Infrastructures exist whereby treatment can be delivered to each of these three groups, and there are many control programmes which have successfully delivered treatments at very low cost.

School children

School children harbour the most intense infections with some of the commonest worms. They are thus the age group most at risk of morbidity and, simultaneously, the major contributors to transmission. Theory and practice indicate that targeting treatment at school children reduces infection levels in the community as a whole\textsuperscript{4,6}. The impact of intervention programmes in terms of averting DALY losses have also been estimated using a population dynamic model: in a community with a 70\% prevalence of \textit{A. lumbricoides} infection in schoolchildren, a sustained chemotherapy programme where only the schoolchildren (60\% of those aged 6–15 years) are treated, could result in aversion of 70\% of the DALY loss in the entire population\textsuperscript{39}.

The fact that children assemble daily in one place, their school, provides an opportunity to deliver mass treatments through an existing infrastructure. The experience of programmes in which teachers have treated children with anthelmintic drugs indicates that school-based programmes are feasible and practicable. In many developing societies, there are more teachers than health workers and more schools than clinics; the education sector provides an already developed and supported infrastructure that might usefully supplement the existing primary health care system. There have been concerns that the education systems and teachers are already too stretched to take on additional tasks, and that teachers and the community would resent the education sector playing a role in health. Carefully monitored school based health and nutrition programmes in
Ghana, Tanzania, India and Indonesia have now shown that the education sector is capable of delivering a simple health package (health education, anthelmintics, sometimes with micronutrients) to large numbers of school children (50,000 to 3 million) without the creation of specific infrastructures. Furthermore, they have shown that teachers perceive this role in health as an acceptable, even welcome extension of their overall role in the community, and that both students and parents concur with this view. Analyses of costs tend to confirm the prediction that such education sector delivery methods are associated with small financial cost. Cost analyses of the Ghana (85,000 children) and Tanzania (125,000 children) programmes indicated that the delivery cost of albendazole was US$ 0.03 per child per annum; for the India programme in Gujarat (2.83 million children), the cost of locally purchased ferrous sulphate, albendazole and vitamin A, delivered as a standard dose twice a year, was US$ 0.50 per child.

**Pre-school children**

Although more research on the benefits of treatment in the pre-school age group is required, a recently concluded consultative meeting sponsored by UNICEF recommended that where the prevalence of infection is high, programmes which currently deliver health care to children aged between 1 year and school age should consider adding periodic anthelmintic treatments to the health care currently provided. Several opportunities for delivery of anthelmintic therapy were identified including: immunization programmes, vitamin A capsule distribution programmes, maternal-child health clinics, the Integrated Management of Childhood Illness programme, and visits to homes by community health workers.

**Adolescent girls and women of child-bearing age**

The contribution of hookworm infection to anaemia is such that all women of child-bearing age (except those in the first trimester of pregnancy) could benefit from periodic treatment in areas where these worms are endemic. There are three critical periods to consider for the intervention to improve or restore iron status in women. The first is around puberty, in preparation for the years of reproduction and greatest economic activity. It is possible that deworming during the pubertal growth spurt could yield a height benefit that a girl would carry with her throughout her life, thus reducing her risk of complications during childbirth, and increasing her physical capacity for work.
The second critical intervention time is around reproductive events, during pregnancy or during the post-partum period. Intervention in pregnancy could favourably influence infant birth outcomes and prevent maternal morbidity and mortality. For example, in Sri Lanka, because hookworm infection is widespread, and maternal anaemia is a major problem, it has been national policy since 1994 to treat all pregnant mothers with a single dose of mebendazole at the first ante-natal clinic visit after completion of the first trimester. Anthelmintic chemotherapy at delivery or immediately post-partum would be the ideal time to reduce the vertical transmission of *A. duodenale*.

Thirdly, if the programme objective is either to improve work efficiency and the economic productivity of women, or to improve their sense of well-being, quality of life and caring capacity, then the goal should be to alleviate iron deficiency and the hookworm load of women throughout their adulthood. Where transmission of hookworm is intense, contacting women only once per pregnancy will probably not achieve this goal, especially in societies where family planning is fairly successful; other strategies such as involving community health workers, or the delivery of treatments through the work place, such as factories or plantations, may have to be considered.

The way forward

All of the above has led to the growing involvement of countries and agencies in programmes that are either aimed primarily at helminth control or that incorporate helminth control as part of an integrated health package. The WHO, in association with its collaborating centres has taken the lead in the technical design of control programmes. In 1996, the WHO issued guidelines on strengthening interventions to prevent helminth infection through schools, as an entry point for the development of ‘health promoting schools’ under its global school health initiative. The World Bank’s World Development report entitled *Investing in Health*, identified school health programmes including deworming as one of five priority public health measures that had the potential to produce substantial gains in health at a modest cost. UNICEF is this year launching a programme to promote deworming in populations at risk. Numerous international and national non-governmental organisations are including deworming in their health promotion strategies. School based delivery is perhaps the most popular approach to anthelmintic distribution, but there is growing interest in incorporating deworming in early child development and maternal and child health programmes.

All this activity will greatly benefit the treated individuals in the short term and lead to enhanced physical and intellectual development. It should also reduce overall levels of transmission so that there is
community-wide benefit in the medium term, while improvements in sanitation should help to sustain the gains in the long term. With appropriately co-ordinated efforts no one need live in a wormy world.

Acknowledgements

The authors are at the Scientific Co-ordinating Centre of the Partnership for Child Development. This international consortium of countries, donors, institutions and individuals was founded in 1992 to explore the cost and effectiveness of school based health interventions. The Partnership is supported by WHO, UNICEF, UNDP, World Bank, the Rockefeller, Edna McConnell Clark and James S McDonnell Foundations, and the Wellcome Trust.

References

1 Stoll NR. This wormy world. J Parasitol 1947; 33: 1–18
2 Chan M-S, Medley GF, Jamison D, Bundy DAP. The evaluation of potential global morbidity due to intestinal nematode infections. Parasitology 1994; 109: 373–87
10 Chan L, Kan SP, Bundy DAP. The effect of repeated chemotherapy on age-related predisposition to Ascaris lumbricoides and Trichuris trichiura. Parasitology 1992; 104: 371–7
14 Crompton DWT, Whitehead RR. Hookworm infections and human iron metabolism. Parasitology 1993; 107: S137–45
17 Stephenson L, Latham M, Adams E, Kinoti S, Perret A. Weight gain of Kenyan school children infected with hookworm, Trichuris trichiura and Ascaris lumbricoides is improved following once- or twice-yearly treatment with albendazole. J Nutr 1993; 123: 656–65


Cooper ES, Bundy DAP. Trichuris is not trivial. Parasitol Today 1988; 4: 301–6


Awasthi S, Petø R, Bundy DAP, Kumar Pandy V, Fletcher RH. Improvement in nutritional status among preschool children in Lucknow, India. A randomised trial of albendazole. King George’s Medical College, Lucknow, India; University of Oxford, UK; and Harvard Medical School, USA. International Clinical Epidemiology Network Annual Meeting, Mexico, February 1997


Nokes C, Bundy DAP. Does helminth infection affect mental processing and educational achievement? Parasitol Today 1994; 10: 14–8


Nokes C, Grantham-McGregor SM, Sawyer AW, Cooper ES, Robinson BA, Bundy DAP. Moderate to heavy infections of Trichuris trichiura affect cognitive function in Jamaican school children. Parasitology 1992; 104: 539–47


Bundy DAP. This wormy world, now. Parasitol Today 1997; 13: 407–9