Multiple helminth infections in children: impact and control

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SUMMARY

Parasitic worm infections are amongst the most widespread of all chronic human infections. It is estimated that there are more than 3 billion infections in the world today. In many low income countries it is often more common to be infected than not to be. Indeed, a child growing up in an endemic community can expect be infected soon after weaning, and to be infected and constantly reinfected for the rest of her or his life. Infection is most common amongst the poorest and most disadvantaged communities, and is typically most intense in children of school going age. As the risk of morbidity is directly related to intensity of infection, it follows that children are the most at risk from the morbid effects of disease. Multiparasite infections are also common in such communities and there is evidence that individuals harbouring such infections may suffer exacerbated morbidity, making children even more vulnerable. Thus, these infections pose a serious threat to the health and development of children in low income countries. For many years, the need to control these infections has lain uncontested, and with the advent of broad-spectrum anthelminthic drugs that are cheap, safe and simple to deliver, control has at last become a viable option for many communities. Furthermore, there is now increased emphasis being placed on a multispecies approach as a cost-effective mechanism to control the morbidity of virtually all the major helminthic infections of humans.

Key words: helminth, multiple infections, school-age child.

THE MAJOR HELMINTH INFECTIONS AFFECTING CHILDREN

There are approximately 20 major helminth infections of humans that all, to some extent, have public health significance (for review refer to Warren, Bundy & Anderson, 1993), but amongst the most common of all human infections are the geohelminthiases. Recent global estimates indicate that more than one quarter of the world's population is infected with one or more of the most common of these parasites: the roundworm, *Ascaris lumbricoides*; the hookworms, *Necator americanus* and *Ancylostoma duodenale*, and the whipworm, *Trichuris trichiura* (Chan *et al*. 1994; Bundy, 1997). In addition, more than 200 million people are estimated to harbour schistosome infections (WHO, 1993).

It is an epidemiological phenomenon that the distribution of helminths amongst hosts is overdispersed. The majority of the hosts harbour few or no worms, whilst a minority of the hosts harbour much larger numbers of parasites (Anderson & Medley, 1985). This fact has clinical consequences for the host, as it is the intensity of infection that is the central determinant of the severity of morbidity (Stephenson, 1987; Cooper & Bundy, 1988). As exemplified in Fig. 1, the age-intensity profile for *Trichuris trichiura* and *Ascaris lumbricoides* is typically convex with maximum intensity at 5–10 years of age. After peak intensity has been attained there is a dramatic decline in intensity to a low level, which then persists throughout adulthood.

A similar profile is apparent for *Schistosoma* infections, but with maximum intensity attained at a slightly later age, usually 10–14 years. A different profile is apparent for hookworm infections, as maximum intensity is usually not attained until 20–25 years (Stephenson, 1987). It is strikingly apparent that it is the school-age child who is particularly at risk from the clinical manifestations of disease. Indeed, it was estimated that, for girls and boys aged 5–14 years in low income countries, intestinal worms account for 12% and 11% of the total disease burden of this age group. An estimated 20% of disability adjusted life years (DALYs) lost due to communicable disease among school children are a direct result of intestinal nematodes (World Bank, 1993).

SO WHAT ARE THE CONSEQUENCES OF THESE INFECTIONS FOR CHILDREN?

Many children in low income countries underachieve and never realise their full potential. The aetiology of

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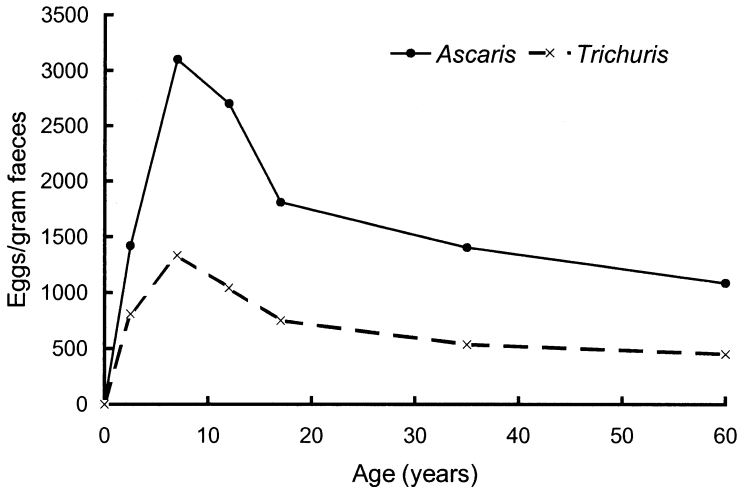


Fig. 1. Age intensity profile of *Ascaris lumbricoides* and *Trichuris trichiura*.

this underachievement is complex since numerous factors experienced during a child's formative years may have a detrimental effect upon development and functional efficiency. However there has been growing recognition of the specific deleterious effects of helminth infections upon both physical and intellectual development. As children suffer most at an age when they are both growing and learning, the entire developmental process is placed in jeopardy.

By far the most common effect on health is a subtle and insidious constraint on normal physical development, resulting in children failing to achieve their genetic potential for growth and suffering from the clinical consequences of iron deficiency anaemia and other nutritional deficiencies: heavy hookworm burdens have long been recognized as an important cause of iron deficiency anaemia (Roche & Layrisse, 1966); intense whipworm infection in children may result in *Trichuris* Dysentery Syndrome, the classical signs of which include growth retardation and anaemia (Bundy & Cooper, 1989); heavy burdens of both roundworm and whipworm are associated with protein energy malnutrition (PEM) (Stephenson *et al*. 1993).

In terms of intellectual development, there is an increasing body of evidence that these infections can have a detrimental effect on cognition and educational achievement in children (Sternberg, Powell & McGrane, 1997). The mechanism by which mental processes are affected is speculative. However, evidence lends itself to suggest that the mechanism is an indirect one. The most plausible mediators are the common sequelae of infection–iron deficiency anaemia (IDA) and undernutrition.

IDA in infants and young children is associated with significantly lower scores on psychological tests (Lozoff, Jimenez & Wolf, 1991; Pollitt *et al*. 1993; Lozoff, 1998). Deficits of 0·5–1·5 standard deviation units in scores on infant development scales or IQ tests for children have been found quite consistently across studies and age groups. Moreover, these effects of IDA during infancy are associated with lower developmental test scores at 5 years of age (Cooper & Bundy, 1988). Similar effects have been shown during school age (Lozoff, 1998), although the relationship is less clear for children with mild IDA (Lozoff, Brittenham & Wolf, 1987). Treatment studies have consistently found improvements in cognitive function following iron supplementation in infancy (Idjradinata & Pollitt, 1993) and in middle childhood (Pollitt, Hathirat & Kotchabhakdi, 1989; Seshadri & Gopaldas, 1989; Soemantri, 1989; Soewendo, Husaini & Pollitt, 1989). IDA also leads to long-term deficits in cognitive functioning (Grantham-McGregor, Walker & Chang, 2000).

Studies of the effect of PEM on cognitive ability are strongly suggestive but not conclusive. Severe PEM is associated with cognitive deficits, but the relationship is not unequivocally causal (Simeon & Grantham-McGregor, 1990). In fact, when comparison groups are controlled for height-for-age (an indicator of long-term undernutrition), the effect of severe bouts of PEM disappears indicating that sustained undernutrition is important when considering effects on cognitive function (Grantham-McGregor, Powell & Fletcher, 1989). This conclusion is supported by studies of mild to moderate PEM, which demonstrate that height-for-age but not weight-for-age (a measure of short-term variations in nutritional input) is associated with development and achievement levels in schoolchildren (Chun, 1971; Powell & Grantham-McGregor, 1980; Jamison, 1986; Moock & Leslie, 1986; Johnston, Low & De Baessa, 1987; Agarwal *et al*. 1987; Florencio, 1988) and in younger children (Powell & Grantham-McGregor, 1985).

The results of intervention (nutritional supplementation) studies are again inconclusive but appear to indicate that mild-moderate undernutrition has concurrent detrimental effects on cognitive function

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(Grantham-McGregor, 1987). Severe malnutrition may lead to long-term cognitive deficits (Grantham-McGregor *et al*. 2000).

Whether helminth infections directly cause cognitive deficits is a matter of debate. The vast majority of over 40 studies demonstrate an association between geohelminthic infection and impaired cognitive or educational abilities (Waite & Nelson, 1919; De Carneri, Garofano & Grassi, 1968; Kvalsvig, Cooppan & Connolly, 1991; Nokes *et al*. 1991, 1992; Boivin *et al*. 1993; Callender *et al*. 1994; Nokes & Bundy, 1994; Simeon, Callender & Wong, 1994; Levav *et al*. 1995; Sternberg *et al*. 1997; Sakti *et al*. 1999). Only a small number of these studies, however, are well designed.

Cross-sectional studies are often flawed due to the proliferation of confounding variables. Infection prevalence is related to age, sex, and socio-economic status (for example, Sakti *et al*. 1999), among other variables. Many apparent differences between infected and uninfected children, particularly differences in educational test performance, disappear when confounding factors are controlled (Berlinguer, Del Trono & Orecchia, 1964; De Carneri *et al*. 1968). So, it is impossible to conclude from associative studies that cognitive impairments have been caused by infection, rather than simply having co-occurred with it.

One positive result to emerge from well designed treatment studies is that found by Nokes *et al*. (1992) in Jamaica. Children with moderate to heavy infections of whipworm showed improvements in working memory (measured by reciting strings of digits forwards and in reverse order) and rapid retrieval of words from long-term memory (verbal fluency) following treatment, as compared with a randomly assigned placebo group. No such improvements were found in visual short-term memory, problem-solving ability, cognitive speed, arithmetic, or verbal comprehension. Simeon, Grantham-McGregor & Wong (1995) studied a similar population with a slightly lower level of infection of whipworm. They found no main effect of treatment on performance on any of the cognitive tests they used, but they did find that wasted children (those with a low weight-for-age) showed improvements in verbal fluency after treatment. Another study using cognitive tests (Watkins, Cruz & Pollitt, 1996*a*), this time in Guatemala, demonstrated improvements in the Sternberg short-term memory scanning test and in simple-choice reaction time (cognitive speediness) following treatment, but only for those children heavily infected with roundworm. Those lightly infected with the same parasite actually showed poorer performance on these tests after treatment. A similar negative effect of treatment was found by Pollit, Perez-Escamilla & Wayne (1991) in Kenya. In this study, children treated for hookworm infection were slower than were a randomly-selected placebo group on a reaction-time task 8 months after treatment. No baseline measures were taken in this study, however, so it is difficult to determine whether the randomization process succeed in producing groups of children with equal abilities before treatment.

Two of the studies using a randomized control design also looked at education-related variables. An improvement in spelling and better attendance was observed with Jamaican children treated for whipworm (Berlinguer *et al*. 1964). However, the effect was evident only for stunted children (those with low height-for-age) with heavy worm burdens. Watkins *et al*. (1996*b*) found no effect of treatment of children with moderate to heavy levels of roundworm on either reading or vocabulary score or on school attendance.

Studies often show an effect in the most heavily infected and affected children, but with such mixed results it is difficult to reach any strong conclusions as to whether helminthiases directly contribute to impairment of cognitive functioning (Dickson, Awsathi & Williamson, 2000). However, it is apparent that a pathway, via infection sequelae, does exist for these infections to at least contribute to this impairment (for a fuller review refer to Drake, Jukes & Sternberg, 2000), and that iron deficiency and PEM secondary to infection may be an important constraint.

Another consideration that should be made with regards to the impact of these infections on development, is that psychological development as a whole covers a broader range of abilities, not only including the more commonly studied domains of cognitive and motor development, but also social and emotional (such as understanding of interpersonal relationships, the development of control over one's emotions) and temperament (such as how children react to new situations). Such domains of psychological development are only just beginning to be included in assessment of the impact of ill health with recent studies of the effect of nutrient deficiency on affect and behaviour (Lozoff *et al*. 1998) and on stress (Fernald & Grantham-McGregor, 1998).

In addition, chronically infected children may become lethargic and less inclined to exert themselves and, as a consequence, not fully benefit from both their domestic and school environments. Given that these years may be only opportunity that many children have for formal education, by not taking full advantage of this they may compromise their social functioning and future potential.

Thus, these infections may also have an insidious and less overt impact upon the developmental process: delays in the development or impairment of these abilities may leave a child lacking in the interpersonal and emotional skills vital to making positive life decisions. This is particularly worrying

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given the current spread of the HIV/AIDS pandemic, and the importance of effective life skills at an early age in avoiding infection.

THE CONSEQUENCES ARE WORSE THAN PREVIOUSLY REALIZED

A growing body of evidence suggests that the effects of infection have tended to be underestimated. One important new factor is that the clinical consequences of infection can manifest themselves at much lower worm burdens than previously thought. Intervention studies have shown that an infection with as few as 10 roundworms is associated with deficits in growth and physical fitness in school-age children and moderate whipworm infections can cause growth retardation and anaemia in children (Cooper *et al*. 1993; Stephenson *et al*. 1933; Thein-Hlaing, 1993). Studies have also demonstrated that even light hookworm infection can lead to anaemia. This is evident not only in the adult population, but also in pre-school and school-children in certain populations (Stolzfus *et al*. 1997, 1998; Olsen *et al*. 1998; Beasley, Tompkins & Hall, 1999; Brooker, Booth & Guyatt, 1999; Brooker *et al*. 1999).

Children, adolescents and pregnant women are particularly at risk from hookworm morbidity as the physiological demands for iron are high during these periods. Evidence suggests that anaemia during pregnancy may adversely influence intrauterine growth rate, prematurity and birth weight. Thus, there may be important maternally-programmed consequences for children (Partnership for Child Development, 1997). In addition, it has been suggested that the clinical consequences of hookworm infection occur at a lower threshold in individuals who have a diet low in bioavailable iron (Crompton & Whitehead, 1993; Tatala, Svanberg & Mduma, 1998). Sadly, this is all too common an occurrence in communities in low income countries.

The second new factor is that multiple species infections may significantly exacerbate morbidity. In some species and regions, people with multiple infections are more common than those with either no infection or a single infection. For example, Crompton & Tulley (1987) listed 47 different protozoan and helminth species found in association with *A. lumbricoides* infections, of which 24 were common. The presence of a variety of human parasites that occur in the same environment each with a high prevalence, increases the likelihood of significant rates of co-infection. Another study estimated that multiple infections including *Plasmodium falciparum*, *Plasmodium malariae*, *Schistosoma haematobium* and three common nematodes occurred in approximately 60% of a Kenyan population (Ashford, Craig & Oppenheimer, 1992). There have been numerous other studies surveying human infections and for a full review of these refer to Petney & Andrews (1998).

Howard, Donnelly & Chan (2000) found that, in general, associations between geohelminth species were positive, which implies that more multiple species infections are observed than would be expected by chance. Predisposition has been demonstrated for all the major helminth infection (Schad & Anderson, 1985; Elkins, Haswell-Elkins & Anderson 1986; Haswell-Elkins, Elkins & Anderson 1987; Holland *et al*. 1989; Bundy *et al*. 1987; Bundy & Cooper, 1988; Bradley & Chandiwana, 1990) and it has been suggested that perhaps certain individuals may be predisposed to multiple infections (Haswell-Elkins *et al*. 1987; Howard *et al*. 2000).

Behavioural factors could be responsible for multiple species infection. For example, *T. trichiura* and *A. lumbricoides* are both transmitted faeco-orally, thus behavioural factors that lead to exposure to and infection with one parasite, may also lead to exposure to and infection with the other parasite (Booth & Bundy, 1995). It has been noted that *A. lumbricoides* and *T. trichiura* infections can cluster within households (Forrester *et al*. 1988, 1990; Chan, Bundy & Khan, 1994) suggesting that individuals in the same peridomicillary environment share some risk factors for each infection. Whether this is caused by genetic factors, behavioural factors or a combination of the two has not been conclusively determined. Analyses do suggest that if there is a genetic basis for predisposition, its effects tend to be overwhelmed by other household-specific effects (Chan *et al*. 1994). However, it is now clear from segregation analysis that genetic factors do partly regulate susceptibility to *S. mansoni* infection (Marquet *et al*. 1996).

But how may multiple infections exacerbate morbidity? Studies suggest that certain morbid effects, for example, reduced cognitive function and reduced haemoglobin levels, may be exacerbated when individuals harbour certain combinations of infections (Robertson, 1992; Behnke *et al*. 1994). Observations indicate that individuals harbouring multiple species infections have higher than expected levels of each infection individually, and thus will be at a higher risk of morbidity (Booth *et al*. 1998). Needham, Kim & Cong (1998) demonstrated that high intensity *A. lumbricoides* infections were significantly more likely to occur with high intensity *T. trichiura* infections than would be expected by chance; children with multiple species infections have higher egg counts of each species than children with single species infections (Brooker, Miguel & Moulin, 2000).

Can we do anything to help these children?

The concept of health is broad. Health can be viewed in terms of the life cycle starting with pregnancy,

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moving through birth, infancy, childhood, the school years, adolescence, adulthood and ageing. Thus development and the benefit of health interventions are cumulative in effect – the benefit in one age group is at least partially dependent on interventions in an earlier age group. Prioritizing interventions at several points across the life cycle is necessary for sustained, high-impact improvements in health outcomes.

The major programmatic constraint in low income countries, where capacity and infrastructure are often lacking, is how to reach people in need. Success in reaching pregnant mothers and infants (under the age of five) has been attained through mother and child programmes and community based IMCI (integrated management of childhood illness) and ECD (early child development) initiatives. Children above the age of five can be most easily reached through school-based health and nutrition programmes, exploiting the existing educational infrastructure. By continuing interventions through the childhood years, the success of ECD and other early interventions can be built upon and strengthened.

Ensuring that children are healthy and able to learn is now recognized as an essential component of an effective education system. This is especially relevant to efforts to achieve 'Education For All' in the most deprived areas, as now more of the poorest and most disadvantaged children have access to school, many of whom are girls. It is these children, who are often the least healthy and most malnourished, who have the most to gain educationally from improved health.

Good health and nutrition are not only essential inputs but also important outcomes of basic education of good quality. On the one hand, children must be healthy and well-nourished in order to fully participate in education and gain its maximum benefits. Thus, programmes which improve health and nutrition can enhance the learning and educational outcomes of school children. On the other hand, quality education, including education about health, can lead to better health and nutrition outcomes for children and, especially through the education of girls, for the next generation of children as well.

Positive experiences by WHO, UNICEF, UNESCO and the World Bank suggest that there is a basic framework that could form the basis for an effective school health and nutrition programme upon which to build. This partnership seeks to Focus Resources on Effective School Health – *FRESH* Start. The framework includes four basic interventions: (1) school-based health policies; (2) provision of safe water and adequate sanitation; (3) skills based health education and (4) school-based health and nutrition services. These interventions are supported by an interactive framework of partnerships.

The cost-effectiveness of mass deworming as part of an effective school health and nutrition programme can be maximized by combining control of both schistosome and geohelminth infections, using two drugs: praziquantel and a benzimidazole derivative. Thus, multiple infections have important implications for the practical design of such programmes. Key to the design of such a strategy is the quantification of the pattern of multiple infections, as this approach will only be cost-effective when these infections are endemic in the same communities.

Preliminary analyses (Bundy *et al*. 1991) demonstrated that the geographical distributions of geohelminth and schistosome infections overlap sufficiently at the national level to warrant consideration for combined control. But it is also known that these infections are unevenly distributed within countries. Thus, methods to identify communities warranting a combined control approach, will enhance the efficacy of this approach.

Geographical information systems (GIS) are being used to develop predictive maps of infection prevalence rates. Focus is, at present, upon an infection atlas of Africa, but expansion is intended. Also, using overall estimates of species associations in different communities and countries, statistical predictive methods are being developed (Howard *et al*. 2000). This methodology is particularly useful when only marginal prevalence data are available.

A rapid assessment tool has been developed that can be used to identify target communities/schools warranting treatment of *Schistosoma haematobium* infections (Lengeler, Sala-Diakanda & Tanner, 1992). This is a questionnaire-based approach using self reporting of blood in urine as a reliable indicator of infection. It may also be possible to identify target communities for treatment of *S. mansoni* infections using a similar approach (Hailu, Jemaneh & Kebede, 1995; Booth, Mayombana & Kilima, 1998). A similar tool does not exist for detection of geohelminth infections. Brooker *et al*. (1999), attempted to predict the prevalence of geohelminth infection using schistosome infection prevalence. This approach proved unsuccessful as results suggested that schistosome and geohelminth infections are independently distributed within countries where they are both endemic. Reported gastro-intestinal symptoms also appear not to be associated with geohelminth infections (Booth *et al*. 1998). Thus, long-term cost-effectiveness of targetted combined control programmes may only benefit from the added expense of parasitological screening.

The combination of impact on physical growth and education gives helminth infection an importance to child development that far outweighs the apparent consequences of infection. A single, oral treatment is sufficient to significantly reduce worm burdens in all but the most intensely infected

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populations. Mass delivery of anthelmintics is one of the most cost-effective, simple and safe school-based health services that can be delivered by trained teachers. Evaluation of large-scale demonstration school health programmes has shown that school-based health services can have an impact on a broad range of health and education outcomes (Partnership for Child Development, 1998). For these reasons deworming has been an essential component of school health programmes in developing countries (Savioli, Bundy & Tomkins, 1992).

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