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Andrew Hall¹
Gillian Hewitt¹
Veronica Tuffrey¹
Nilanthi de Silva²

¹ Centre for Public Health Nutrition, School of Integrated Health, University of Westminster

² Faculty of Medicine, University of Kelaniya

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A review and meta-analysis of the impact of intestinal worms on child growth and nutrition

Andrew Hall¹, Gillian Hewitt¹, Veronica Tuffrey¹ and Nilanthi de Silva²

¹Centre for Public Health Nutrition, University of Westminster, 115 New Cavendish Street, London W1W 6UW, U.K.

² Faculty of Medicine, University of Kelaniya, Ragama, Sri Lanka.

Author for correspondence: Andrew Hall, Centre for Public Health Nutrition,
University of Westminster, 115 New Cavendish Street, London W1W 6UW
Tel: 0207 911 5000 E-mail: a.hall04@westminster.ac.uk

Abstract

More than a half of the world's population are infected with one or more species of intestinal worms of which the nematodes *Ascaris lumbricoides*, *Trichuris trichiura* and the hookworms are the most common and important in terms of child health. This paper: a) introduces the main species of intestinal worms with particular attention to intestinal nematodes; b) examines how such worms may affect child growth and nutrition; c) reviews the biological and epidemiological factors that influence the effects that worms can have on the growth and nutrition of children; c) considers the many factors that can affect the impact of treatment with anthelmintic drugs; d) presents the results of a meta-analysis of studies of the effect of treating worm infections on child growth and nutrition; e) discusses the results in terms of what is reasonable to expect that deworming alone can achieve; f) describes some important characteristics of an ideal study of the effects of deworming; and g) comments on the implications for programmes of recommendations concerning mass deworming.

Keywords

Intestinal worms, anthelmintics, children, growth, nutrition

Key messages

- The effects of intestinal worms depend on the species, the mixture of species, the duration of infection and on the number of worms.
- The distribution of worms among hosts is highly skewed so that only a minority of infected individuals have moderate to heavy infections and are likely to be diseased.
- The impact of infections will also depend on the size and nutritional status of the host.
- Treating worms can lead to improvements in growth and nutritional status but deworming alone does not treat any underlying nutritional deficits that have been caused or made worse by worms, so extra energy, protein and micronutrients are required.

1. Introduction

Parasitic worms are among the most common and widespread infections of humans in the world today. Using recent estimates of the prevalence of the four main species of intestinal nematode worm (de Silva et al., 2003) a simple calculation that assume the probability of infection with one worm is independent of infection with another, indicates that about 48% of the 5 billion or so people living in the developing world are infected with at least one species, while almost 10% are infected with at least two species. But, if some 2.3 billion people in the developing world are infected with intestinal nematode worms, why isn't disease due to worms more common, and why don't they seem to have a greater and more noticeable impact on the health of children? This review will attempt to explain why, it will review the studies that have been done to examine the impact of treating intestinal nematode worms on children's nutritional status and growth, and it will examine the scientific and experimental problems with estimating the impact that worms in general have on human health.

1.1 The gastro-intestinal ecosystem

The human intestinal tract provides a protected habitat for several hundred species of viruses, bacteria, yeasts, protozoa and worms. All the organisms that live in the intestinal ecosystem are parasites, because they are dependent for their existence on their host, and the basis of this dependence is usually nutritional (Hall, 1985). The parasitic life-style is highly successful for worms in general mainly because, once established within a host, there are no predators and life is a sheltered steady state with a constant supply of nutrients that is sustained by the host's homeostatic mechanisms.

Because the gut is a cavity within the host, it is said to be immunologically privileged, as the organisms living there are not exposed to the full force of the human immune system. Nevertheless, intestinal worms do elicit an immune response, and hookworms and whipworms in particular come into contact with both the cellular and humoral immune systems to elicit a Th-2 responses and cause a rise in the concentration of IgE (Else, 2005). But the fact that intestinal worms persist and are not expelled from the gut indicates

that they are able to evade these immune responses, although the mechanisms by which they achieve this are unclear.

The only important non-specific barrier to infection is hydrochloric acid, secreted as ions into the stomach lumen by the parietal cells in the gut wall. Although this acid can kill infectious stages of many potential pathogens, paradoxically it is also a necessary stimulus for the establishment of many parasites: exposure to acid is required for the excystment of *Giardia duodenalis* (al-Tukhi et al., 1991, Hautus et al., 1988) and may be a necessary stimulus for the eggs of *Ascaris lumbricoides* to hatch, along with warmth and exposure to bile salts. But once in the intestine, the site where the worms come to maturity, all parasites of the gut have a body surface that is resistant to the action of the host's digestive enzymes, while some worms have developed specific anti-enzymes (Uglen and Just, 1983), presumably for self-protection. The role of anti-enzymes in causing malnutrition is putative rather than proven, and it seems most likely that they act locally to prevent damage to the worms' surface by host enzymes, rather than being secreted to have a widespread effect in the gut and thus perhaps on human nutrition.

The infectious stages of parasites have an easy way to enter their host, usually through the mouth as a contaminant of food, water or fingers, while the next generation leaves the body in faeces through the anus in the form of spores, cysts, eggs or larvae. There are exceptions: a few parasites of the gut enter the body through the skin, notably the larvae of hookworms and *Strongyloides stercoralis*.

The major problem for parasitic worms is to get from one host to another, a journey that is facilitated in several different ways:

- by producing large numbers of infectious stages to increase the chances of infecting a new host; a fertilised female *A.lumbricoides*, for example, may produce up to 200,000 eggs a day (Sinniah, 1982), therefore millions in a life-time;
- by producing resistant infectious stages that can withstand adverse conditions; the eggs of species of *Ascaris* can survive for several months or years in warm, humid and sheltered conditions (Gaasenbeek and Borgsteede, 1998), and are resistant even to 10%

formalin (Sandars, 1951) though not to exposure to ultra-violet light or to desiccation (Crompton, 1989);

- by infecting an intermediate host in which the parasite both multiplies and is dispersed, a feature of the life-cycle of many trematodes, a group of flatworms whose species often reproduce in snails from which are released larval stages that are infectious to humans ;
- by infecting or encysting on foods that are consumed by a new host (Fried et al., 2004);
- by the behaviour of infected people that puts others at risk of infection, such as defecating in the open, so that infectious stages are spread in the environment (Kilama, 1989);
- and the behaviours that put people at risk of infection, such as pica (Geissler et al., 1998); by using fresh human faeces (sometimes called 'nightsoil') as a fertiliser (Needham et al., 1998, Pan et al., 1954); and by poor personal hygiene.

Because the gastro-intestinal ecosystem offers such a rich habitat it has been colonised by an enormous number of different species. The next section introduces the major species of worms that live in the human gastro-intestinal tract.

1.2 Groups of intestinal parasitic worms that infect humans

The variety of general and specific names given to worms can be quite confusing to a novice (see Box 1). The terms 'helminths' and 'worms' are generic names for metazoan (multicellular) parasites that are classified by helminthologists into two main Phyla:

- Nematoda: the nematodes or roundworms, such as *Ascaris lumbricoides* and *Trichuris trichiura*;
- Platyhelminthes: the flatworms, which contain two important Classes of parasites of humans:
 - Trematoda: the flukes, such as *Fasciolopsis buski* and *Metagonimus yokogawa*;
 - Cestoidea, sub-class Eucestoda: the tapeworms, such as *Taenia saginata* and *Diphyllobothrium latum*.

Box 1 *How worms are named*

Worms go under a variety of general and specific names derived from different languages, but mostly old English, Latin or Greek. 'Worm' is derived from the old English word *wyrm*, meaning a snake or a dragon. 'Worm' is also associated with the Latin *vermis* from which comes the English words vermicide and vermifuge, a drug for treating worms. The generic term 'helminths' is an English word derived from the Greek word for worms, *helmins*. From this root is derived the term anthelmintic (sometimes anthelminthic or antihelminthic), a drug to treat worms. The name of the phylum Platyhelminthes combines the Greek terms *platys*, meaning broad or flat, and the word for worm. The Platyhelminths include two groups: the tapeworms (Old English 'tape' meaning tape, combined with 'worm') or cestodes (derived from the Greek word *kestos* meaning a strap); and the flukes (Old English term derived from the name for a type of fish called a plaice or flounder, which the worms look like) also called trematodes (derived from the Greek word *trema* meaning orifice or hole and *eidos*, meaning 'in form'). The Phylum Nematoda (derived from the Greek *nema*, a thread, and *eidos*, meaning 'in form') are classified as helminths (but not Platyhelminths) as they are roundworms (derived from old French *ronde* meaning round), not flat worms. Each species has a name in Latin that is a noun (which takes an upper case first letter) followed by an adjective (which takes a lower case first letter). For example the Latin name *Ascaris lumbricoides* is derived from the Greek word *Askaris*, meaning intestinal worm, and the Latin word *lumbricus*, meaning worm-like. The worm was given its name in 1758 by Carolus Linnæus, the father of nomenclature, who apparently had not heard of tautology.

Over 340 species of helminths have been recorded in association with humans (Coombs and Crompton, 1991) but most are rare zoonoses – infections of animals that can be contracted by humans. Table 1 lists the names of the most common species of helminths that live in the human intestine. The following section describes the life cycles of the most common species of intestinal flukes, tapeworms and roundworms.

Insert Table 1 here

1.2a Flukes or trematodes

The two main species of intestinal trematode that infect humans listed in Table 1 are not widespread, although *Fasciolopsis buski* occurs focally in south-east Asian countries such as Thailand and the Philippines (Waikagul, 1991) and in the Indian sub-continent (Gilman et al., 1982, Chandra, 1984). *Fasciolopsis buski* is a zoonosis, and usually infects dogs and pigs, two animals closely associated with humans (Mas-Coma et al., 2005). A study in China reported an association between malnutrition and infection with flukes including *F. buski*, but the prevalence of this species was relatively low and the main pathogenic species was judged to be *Schistosoma japonicum* (Zhou et al., 2005).

Some 16 species of *Echinostoma* have been reported to infect humans (Carney, 1991, Huffman and Fried, 1990), which makes it the most common genus of intestinal fluke, but another seven species of gut flukes from a variety of Trematode families have been recorded including the Fasciolidae, Heterophyidae, Lecithodriidae, Microphallidae, Paramphistomatidae and Plagiorchiidae (Waikagul, 1991). They are all zoonoses: infections of humans occurs by eating freshwater fish or shellfish, and the normal hosts are fish-eating animals such as cats and birds. Infections in humans are mainly found in adults in Asia who eat undercooked intermediate hosts such as crabs, frogs or fish, or in children who swallow metacercariae that have encysted on vegetation, such as water caltrop.

Infections with intestinal flukes are not common, even among adults, and are rarer still among children, so there is no known association with malnutrition.

The members of the order *Schistosoma* are not included in this review because they are not parasites of the intestinal lumen: they live in the portal

blood vessels around the gut (*S.mansoni* and *S.japonicum*) or urinary bladder (*S.haematobium*).

1.2b Tapeworms or cestodes

Of the most common tapeworms of humans, the three species of *Taenia* tend not to be found among children as they are transmitted by eating undercooked beef (*T.saginata*) or pork (*T.solium* = *Taeniarhynchus solium* and *Taenia asiatica*) (Macpherson, 2005, Eom and Rim, 1993). These foods are not commonly eaten by poor children, or are proscribed in some parts of the world. The adult worms live in the small intestine and release their eggs in packets called proglottides, a living section that breaks off the posterior end of a growing worm (Pawlowski and Schultz, 1972). The proglottides of *T.saginata* are motile and can crawl away from a human stool deposited on the ground (see Figure 1), whereas the proglottides of *T.solium* do not show this activity. This behaviour occurs because cattle do not eat human faeces, but pigs do. When the eggs of *Taenia* species are swallowed by a suid or bovid species, they hatch, penetrate tissues and develop in muscles or organs to become infective cysticercoids. Humans become infected by eating raw or undercooked beef or pork. Infections can be common among people who habitually eat undercooked meat, such as ethnic groups that live in the Rift Valley of East Africa (Hall et al., 1981). Because the eggs are passed in packets rather than loose in the faeces, infections can be missed during the microscopical examination of faecal samples (Hall et al., 1981).

Insert Figure 1 here

The main concern for disease in humans is the possibility that the eggs of *T.solium* may hatch in the human intestine and develop in tissues to cause cysticercosis. If this happens in the brain it can lead to epilepsy (Newell et al., 1997). When pigs infected with *T.solium* were given to appease guerrillas fighting the government in west New Guinea, there was an outbreak of cysticercosis. This came to attention when people with severe burns appeared at hospitals: they had experienced an epileptic fit when sleeping next to a fire for warmth at night and had fallen into the flames (Gajdusek, 1978).

The effect of tapeworms in the intestine is minimal, probably because their relative mass is small in comparison with their host. It is also thought that the presence of existing worms may perhaps inhibit the establishment of additional worms, though this is hard to prove without deliberately infecting people. There is no known association between infections with *Taenia* spp and malnutrition in children.

Hymenolepis nana is a widespread parasite of children, but the reported prevalence rarely exceeds 20% and is usually less than 5% (Khalil et al., 1991, Mason and Patterson, 1994, Sirivichayakul et al., 2000). The worm can persist by means of autoinfection, a process in which eggs hatch and mature in the human gut to form adults, without passing into the environment in the normal way to infect an insect intermediate host.

Hymenolepis diminuta is usually a parasite of rodents, but it is found in children in situations in which they come into contact with rat or human faeces containing the worms' eggs.

Both species of *Hymenolepis* are associated with malnutrition, in that they tend to occur amongst children living in poor and unhygienic communities, but there have been no studies looking at the impact of treatment to suggest that they cause malnutrition.

Diphyllobothrium latum is a notable tapeworm because it selectively absorbs vitamin B₁₂ from the diet of its host or may interfere with absorption, which occurs only in the last third of the ileum; this can lead to pernicious anaemia (Nyberg, 1963). Infections occur by eating raw freshwater fish containing a plerocercoid larva, and were once common in Scandinavian countries such as Finland (Raisanen and Puska, 1984). This species has been reported all over the world, but mostly as curious case reports. It is not a common cause of anaemia in young children mainly because fish is an expensive food, and in most communities it is not commonly eaten raw, especially by children.

1.2c Roundworms or nematodes

Of the six species of nematode worms listed in Table 1, *Enterobius vermicularis* is found worldwide but is rarely a cause of serious disease, and is more a cause of irritation. The female worms lay their eggs around the anus

at night. This causes itching and pruritis that may occasionally lead to perianal sepsis in young children (Mahomed et al., 2003), probably because they scratch themselves. Infections have been reported to cause enuresis (Otu-Bassey et al., 2005) and are very rarely associated with appendicitis (Arca et al., 2004).

Enterobius vermicularis tends to be most common among very young children, especially in kindergartens or among children living in institutions, probably because their personal habits are not well developed and they are in close physical contact with other children (Remm, 2006, Song et al., 2003). It is a difficult infection to diagnose efficiently because the eggs are not often seen in faeces, so it is necessary to press sticky cellophane tape over the peri-anal skin of a child, usually after a night's sleep when the worms have laid their eggs, and examine the tape under a microscope (Celiksoz et al., 2005). The itching may affect a child's sleep, but is not known to be a cause of malnutrition or poor growth.

Infections with *Strongyloides stercoralis* are also associated with poor hygiene, close contact between people, and a lack of sanitary facilities. Infections have been reported among children in nursery schools and among adults in psychiatric institutions (Braun et al., 1988, Gatti et al., 2000). The worm can persist by a process of auto-infection in which larvae hatch in the large intestine and burrow directly into the gut wall, so emulating a naturally acquired infection (Schad, 1989).

Infections with *S.stercoralis* can be transmitted directly from person-to-person by exposure to fresh faeces in the immediate living environment. A study in Bangladesh found that infections with *S.stercoralis* in people living in an urban slum were associated with households that lacked a latrine and had an earthen floor which may help larvae to survive (Hall et al., 1994). But when these factors were controlled for, the aggregation of infections may have been due not only to shared risk factors, but to a genetic predisposition that could also have contributed to infection (Conway et al., 1995).

Although hyperinfections with *Strongyloides stercoralis* can be dangerous in immunocompromised patients (Keiser and Nutman, 2004), such as those being treated with immunosuppressants (Schaeffer et al., 2004) or in the elderly, little is known about how many children are infected in the world

today, so the worm's status as a cause of malnutrition and poor growth is unknown.

The four main nematode worms most commonly associated with malnutrition and disease in children are *Ascaris lumbricoides*, *Trichuris trichiura* and both species of hookworms, *Ancylostoma duodenale* and *Necator americanus*. These worms are sometimes called soil-transmitted helminths. As this term refers to their mode of transmission, the generic term intestinal nematodes will be used here, which infers direct consequences for human health, and is perhaps more informative.

Ascaris lumbricoides is the largest intestinal nematode worm to infect humans. An adult female *A.lumbricoides* typically weighs between 4 and 7 g, but can weigh up to 9 g and grow as long as 40 cm. Male worms are smaller, and weigh 2 – 3 g. Adult worms usually inhabit the jejunum (Crompton, 1989) where they feed on intestinal contents, but worms may be found higher and lower in the gut when present in large numbers, perhaps because of competition for living space. Worms may sometimes migrate into unusual sites such as the bile or pancreatic ducts, which they can block and cause acute and life-threatening disease (Ferreira and Cerri, 1998, Sandouk et al., 1997). Adult *A.lumbricoides* have a tendency to wander if irritated and worms have been extracted from the nose and Eustachian tube (Fagan and Prescott, 1993, Jain and Pahuja, 1988).

Adult *A.lumbricoides* maintain their position in the intestine by swimming against the flow of food, and when they die, they are carried out of the body in the faeces. *Ascaris lumbricoides* is the only intestinal nematode worm that is easily seen and identified in faeces, and is the only species of nematode for which anthelmintic treatment is visibly successful. This was the basis of a long-running Japanese family planning programme:^a because the expulsion of *A.lumbricoides* from the gut offered manifest evidence of the effectiveness of treatment it provided an entry point to households to encourage women to use family planning.

An adult female *A.lumbricoides* may produce up to 200,000 eggs a day (Sinniah, 1982) in a life-span of 12 – 18 months (Anderson and May, 1991),

^a The Japanese Organization for International Cooperation in Family Planning (JOICFP)

but there is good evidence of both density dependent fecundity (Hall and Holland, 2000) as well as geographical variation in the number of eggs produced per female worm (Hall and Holland, 2000). This means that worms produce fewer eggs when there are many present in the gut, and that there is not a linear relationship between the number of worms in a host and the concentration of eggs in faeces. The consequence is that the concentration of eggs in a faecal sample from a Bangladeshi child, for example, is not necessarily equivalent in terms of worm burden to the same concentration of eggs in a sample from an Iranian child (Hall and Holland, 2000). As any given concentration of eggs in faeces may not reflect the same number of worms in different parts of the world, it means that the use of fixed ranges of egg counts to classify the intensity of infection with intestinal nematode worms is scientifically dubious. This is discussed in more detail in Section 2.

Freshly excreted *A.lumbricoides* eggs are not immediately infectious and take 10 – 14 days to embryonate in the environment at 30 C, or about 50 days at 17 C (Pawlowski and Arfaa, 1984). This means that old faeces are a source of infection, not fresh faeces, and the soil on which they lie may no longer bear evidence of faecal contamination. A new infection occurs when mature eggs are swallowed as a contaminant of food or fingers. When an egg comes into contact with bile acids, the larva breaks out of the egg case and burrows through the intestinal wall. After a few days migration through the blood stream to the liver and then to the lungs, the developing larvae break into the alveoli and are coughed up and swallowed. Large numbers of larvae can cause a verminous pneumonia (Tomashefski et al., 1989, Valentine et al., 2001, Gelpi and Mustafa, 1968). The larvae pass through the stomach and into the small intestine for a second time, where they grow and mature to become adults. Although this migration through tissues exposes the immune system to *Ascaris* antigens and stimulates an immune response, it does not seem to lead to protective immunity, at least not in all individuals, although some individuals may develop partial immunity (see Section 2.4).

The adults of *Trichuris trichiura* live in the large intestine and caecum (Bundy and Cooper, 1989). These nematode worms insert their whip-like anterior end into the gut wall and secrete enzymes and a specific protein that causes a syncytium to form (Drake et al., 1994), which provides an easily

ingested liquid food. The penetration of the worm into tissues also causes inflammation and bleeding so that, when large numbers of worms are present, they can cause dysentery and even rectal prolapse (Bundy and Cooper, 1989). Each female worm produces 3,000 – 20,000 eggs a day (Bundy and Cooper, 1989). The eggs mature in the environment to form an infectious larva within the egg shell in about 10 – 14 days. When a mature egg is swallowed the larva hatches from the egg in the stomach and is propelled down the gut by peristalsis to the worm's habitat in the large intestine.

The two main species of hookworm that infect humans, *Ancylostoma duodenale* and *Necator americanus*, are usually considered together, for two reasons. First, because they mostly now have an overlapping geographical distribution and occur worldwide, even if their origins were in the old and new world respectively. Second, the eggs of each species cannot be told apart when examined under a microscope, so only a diagnosis of hookworm can be made. It is necessary either to hatch the eggs and examine the larvae to tell which species is which, or to expel adult worms from the gut and recover them from the faeces. Both of these procedures are difficult and the first carries a risk of infection.

The eggs of both species of hookworm are passed in the faeces. A female *A. duodenale* is estimated to lay 10,000 – 25,000 eggs a day and a female *N. americanus* 5,000 – 10,000 eggs a day (Pawlowski et al., 1991). Again, like *A. lumbricoides*, the average number of eggs produced per female worm declines as the number of worms increases, a mechanism believed to contribute to the stability of worm populations (Bundy, 1990) but which may also serve to help prevent massive infections occurring. Hookworm larvae hatch out onto the soil within 48 - 96 hours of being passed in the faeces, although the speed of maturation depends on the temperature and humidity (Smith, 1990). The larvae do not feed, so have a finite life-span measured in a few weeks, again depending on the temperature, the degree of humidity to prevent desiccation, and whether the larvae are shaded from sunlight or not, such as by vegetation (Smith, 1990). Hookworm larvae are thought to survive longest on light, sandy soil rather than on heavy, clay soil, and in places where the relative humidity is high (Mabaso et al., 2003).

Infection with both species of hookworm occurs when the third stage larvae on the soil come into contact with bare skin. The infectious larvae burrows through the epidermis by a process of mechanical penetration facilitated by secreted protease enzymes (Salafsky et al., 1990). In large numbers this can cause an allergic reaction called “ground itch” (Gilles, 1990). Infections with *A. duodenale* can also occur if the larvae are swallowed (Schad, 1990).

Once in the human body, hookworm larvae migrate through the blood system and heart to the pulmonary blood vessels, where they bore into the alveoli. The action of the cilia lining the bronchioles carries the larvae upwards, into the oesophagus, where they are swallowed, pass through the stomach, and reach the small intestine. The worms take about 4 - 5 weeks to mature and start producing eggs, called the pre-patent period. There is circumstantial evidence that larval worms may get into breast milk, because hookworm eggs have been seen in the faeces of infants too young to have been exposed to larvae (Schad, 1990).

The buccal cavity of both species of hookworms that infect humans contains sharp plates or ‘teeth’ used to grasp and cut gut tissue to enable the worms to suck up blood and tissue fluids (Roche and Layrisse, 1966). Both species of hookworm secrete an anticoagulant to maintain the flow of blood (Roche and Layrisse, 1966, Hotez and Cerami, 1983). It has been estimated that a single *A. duodenale* causes blood loss of 0.2 ml per day (range 0.14 – 0.26 ml) compared with 0.04 ml per day (range 0.02 – 0.07 ml) by *N. americanus* (Roche and Layrisse, 1966). When expressed in terms of the number of worms needed to lose 5 ml of blood each day, this corresponds to 25 *A. duodenale* and 110 *N. americanus* (Pawlowski et al., 1991). Some of the blood and iron ingested by hookworms is excreted into the host’s gut, and is available for absorption lower down the intestine. It has been estimated that as much as 40 – 60% of the iron lost into the gut may be reabsorbed by anaemic people (Roche and Layrisse, 1966). Whether or how quickly any given individual develops anaemia will depend on five factors: the number of worms; the duration of infection (see Section 2.3); the initial haemoglobin concentration; the size of the existing reserves of iron in the bone marrow;

and, most importantly, the amount and bioavailability of iron in the diet (Crompton and Whitehead, 1993, Gilles, 1990).

1.3 How worms may affect human nutrition and growth

There are several mechanisms by which intestinal nematodes could affect the nutritional status of their host:

- By feeding on the contents of the host's gut, including the host's secretions that make up the exoenteric circulation;
- By feeding on host tissues, including blood and serum, that leads to a loss of iron and protein;
- By causing maldigestion or malabsorption of nutrients;
- By inflammatory responses that lead to the production of substances that may affect appetite and food intake, or substances that modify the metabolism and storage of key nutrients such as iron;
- And through contingent responses to infection, such as fever, leading to an increased metabolic rate; by causing hypertrophy of muscles; and by immune responses to infection, all of which result in the diversion or use of nutrients and energy for purposes that would not have been necessary had worms not been present.

All intestinal parasites obtain their nutrients either from the food and intestinal secretions of their host, or from their host's tissues and body fluids. The nutritional needs of parasites are relatively small compared with a well nourished host, mainly because their relative biomass is small (see Box 2). This means that worms such as *A.lumbricoides* only take a relatively small proportion of the host's food from the gut. A study of tapeworms in protein malnourished rats indicated that the amount of protein in worms was only about 1% of the total protein intake, even if there were enough worms to fill the small intestine (Hall, 1983). Although worms do not have an aerobic metabolism and are relatively wasteful of substrates to generate energy, it is also likely that the worm's excretory products are absorbed, metabolised and excreted by the human host.

Box 2 The nutrition of worms

There is a common belief that worms make children thin by consuming the food in their intestine or that they increase children's weight by their presence.(SC/UK, 2004) This is a fallacy because the biomass of worm tissue is relatively small in comparison with the biomass of an infected child. For example a female *Ascaris lumbricoides*, which is the largest intestinal nematode worm that infects humans, has an average weight of some 3.2 g and a maximum of 9.0 g. Male worms are half the size. A study of the worm burdens of 268 infected children aged 4 – 10 years old found an average of 23 *A.lumbricoides* per child which weighed an average of just under 50 g. This was 0.3% of the average weight of the children. If 70% of the weight of worm tissue is metabolically active (excluding the chitinous exoskeleton and the pseudocoelomic fluid), and if the metabolic rate and need for energy of the worm is the same as its homeothermic host (77 kcal/kg/day), then a biomass of 50 g would require about 2.7 kcal of energy a day. As helminths have an anaerobic metabolism which only generates about 5% of the energy as aerobic metabolism, this biomass of worms would require some 54 kcal, equivalent to 13 g of glucose, a day. However as the metabolic by-products of the worm's metabolism are likely to be absorbed and metabolised by the host, in whom they could produce energy, the inefficiency of energy production by worms may be mitigated. Some unique metabolites of *A.lumbricoides* can be detected in human urine in proportion to the number of worms in the host (Hall and Romanova, 1990). These rough estimates indicate that the nutritional needs of most worm burdens are small in relation to a child host, though during a severe shortage of food, the loss of any nutrients to a moderate or large worm burden may exacerbate undernutrition.

The impact of worms' nutritional requirements may be more significant to a host if the worms feed directly on host tissues, because the physical damage they do may have important consequences, in addition to the effects of nutrient losses due to feeding. For example when hookworms move from a site at which they have been feeding, it may continue to bleed into the gut as a result of the persistent effects of the anticoagulant secreted from the worm's salivary glands (Hotez and Cerami, 1983). Moderate to heavy infections with hookworm are strongly associated with anaemia (Roche and Layrisse, 1966) which has consequences for growth (Stephenson et al., 1993a), physical fitness (Stephenson et al., 1993a, Latham et al., 1990b, Stephenson et al., 1990) and worker productivity (Gilgen et al., 2001, Selvaratnam et al., 2003, Hunt, 2002). The feeding of hookworms can also cause a loss of blood proteins and the development of hypo-albuminaemia (Gilles, 1990).

Maldigestion and malabsorption may occur as a result of physical damage to the gut surface. The presence of moderate burdens of *Ascaris suum* in experimentally infected pigs has been shown to cause flattening of villi as well as villous atrophy and fusion (Martin et al., 1984), all of which could lead to a loss of brush border enzymes and a reduced surface area for digestion and absorption.

Damage to villi might be expected to lead to the loss of lactase. A study of African children infected with intestinal parasites, including *A.lumbricoides*, did not find evidence of lactose malabsorption (Gendrel et al., 1992) although this may be a result of a failure of the study to take into account the worm burden (see Section 2.3). Another study, of Panamanian children, did find differences between groups of infected and uninfected children in the results of hydrogen breath tests, an indicator of lactose malabsorption (Carrera et al., 1984).

Another possible cause of malabsorption could be bacterial overgrowth of the small intestine due to the presence of worms, though this is more commonly associated with infections such as *Giardia duodenalis* (de Boissieu et al., 1996, Farthing, 1993, Müller and von Allmen, 2005, Tandon et al., 1977).

A loss of appetite has been reported as a consequence of worm infections (Easton, 1999, Symons, 1985, Hadju et al., 1996) but it is hard to

study, because it would mean leaving some infected children untreated while others were given an anthelmintic. However several studies have measured improvements in the appetite of children after treating worms (Hadju et al., 1996, Latham et al., 1990b, Stephenson et al., 1993a), which has provided quite convincing evidence of an important mechanism by which worms can impair children's nutrition and growth.

The contingent responses to infection, which have been described in a previous review (Hall, 1985), lead to a waste – or at least an unnecessary diversion – of resources as a result of the physical and immunological responses to infection. These are hard to quantify in humans, so experimental animals are often used. For example, experimental infection of pigs with moderate numbers of *A.suum*, a species very similar to *A.lumbricoides* that can also infect humans, has been shown to lead to an increase by 50 – 100% in the wet weight of the small intestine compared with uninfected controls, mainly due to hypertrophy of the *tunica muscularis* (Stephenson, 1987). This is likely to be in response to the need for increased muscularity to push food past worms in the small intestine by peristaltic contractions. Histological cross-sections of the mucosa also show changes in tissues in addition to the flattened villi described above: the *lamina propria* becomes infiltrated with mast cells and eosinophils as a result of immune reactions to the presence of worms in the intestine, while goblet cells show hyperplasia as a result of producing more mucus, perhaps to try to protect the villi from erosion (Stephenson, 1987, Stephenson et al., 1980a). These may be usefully adaptive and protective responses to infection, but they represent a diversion of nutrients that should not be necessary and could be better used for growth if they happen in an already undernourished child.

1.4 Design of studies to estimate the impact of worms

The main problem with studying the impact that worms have on child growth and nutrition has been touched upon in the previous section: the need for untreated controls. If worms impair growth, and if treating worms leads to extra or catch-up growth, then it is necessary to measure the difference that treatment makes between treated and untreated subjects, not just the absolute amount of growth that occurs after treatment. This is because some

amount of growth and weight gain should occur naturally in all children, unless they are severely undernourished or have a hormonal disease.

It could be argued that it is enough to express weight gain as a change in proportion to a reference value, such as a higher z-score of weight-for-height, or a greater percentage of the median value. But such improvements in anthropometric status could occur as a result of secular changes in the food supply, or as a result of better health because of seasonality in the transmission of other diseases, such as malaria and diarrhoea. Concurrent and untreated controls are essential to the validity of the conclusions of any study of the impact of treating intestinal worms on child growth and nutritional status and are an important criterion for including any study in a meta-analysis.

1.5 Aims

The aim of this review is:

- To describe the epidemiological factors that influence the impact that intestinal worms have on human nutritional status and growth;
- To describe the factors that affect the impact of anthelmintic treatment;
- To undertake a meta-analysis of the effects of intestinal worms on children's nutritional status and growth.

2. Factors affecting the impact of intestinal worms

In order to understand the impact that intestinal nematode worms have on the nutritional status and growth of children by any of the mechanisms proposed in Section 1, it is necessary to understand the factors that are likely to influence the degree or magnitude of their effects.

2.1 Species of intestinal worm

The most important species in terms of disease are *Ascaris lumbricoides*, *Trichuris trichiura* and the hookworms. These worms live in different parts of the intestine, differ in the route they take to reach their adult habitat, and feed in different ways. This has been described in Section 1.2.

Although *A.lumbricoides* is undoubtedly the most common species worldwide, it is very hard to distinguish from *A.suum* (Crompton, 1989). It is quite likely that both species occur together, especially in places where pigs are allowed to roam freely in their search for food in an environment inhabited by people (Maruyama et al., 1997, Kofie and Dipeolu, 1983).

Although the two hookworm species are considered together because there is no easy way to tell them apart, there is evidence that *A.duodenale* is more pathogenic than *N.americanus* because it consumes more blood per worm (Roche and Layrisse, 1966). As well as measurements of blood loss using radioactive isotopes (Roche and Layrisse, 1966), there is epidemiological evidence from a study of schoolchildren in Pemba, a small Tanzanian island where both types of hookworms occur, that in schools where the prevalence of *A.duodenale* is high there may be more anaemia and iron deficiency than in schools where *N.americanus* is the predominant species (Albonico et al., 1998).

The conclusion is that different species will have different effects on the nutritional status and growth of children.

2.2 Prevalence of infection

The first important epidemiological parameter that describes the potential effect of worms on human health is the proportion infected, or prevalence. Infections are usually diagnosed by seeing the characteristic eggs of each species of worm in faeces examined under a microscope, which simply indicates that there is present in the gut at least one sexually mature female and one male worm. The exception is *A.lumbricoides*, because unfertilised female worms can produce infertile or “decorticated” eggs; they can be identified because they are longer and narrower than fertilised eggs (Crompton, 1989, WHO, 1994a).

Infections with intestinal worms may therefore be missed if there are only female worms present, or only male worms, or only immature worms. Such infections are not clinically important, but they will lead to an underestimate of the prevalence

Infections may also be missed if an insensitive method of diagnosis is used, such as a direct faecal smear, and if the concentration of eggs in faeces is low. A study in Bangladesh found that some 8% of infections with *A.lumbricoides* were missed when infections were diagnosed using a moderately sensitive ether sedimentation method (Hall, 1981) and compared with a diagnosis made by expelling worms using an effective anthelmintic drug (Hall et al., 1999).

Table 2 shows the range in numbers of eggs estimated to be produced daily by a female worm of each species. They suggest that the sensitivity of diagnosing a light infection of a few worm varies between species, probably in the rank order *A.lumbricoides*, *A.duodenale*, *T.trichiura* and lastly *N.americanus*.

Insert Table 2 here

Infections with the three main types of intestinal worms number among the most common infections of children in the world today. Table 3 presents some recent estimates of the numbers of people infected with *A.lumbricoides*, *T.trichiura* and the hookworms, by age range. Table 4 presents recent estimates of the prevalence of these infections in young school-age children, aged 5 – 9 years. This age group is particularly likely to have moderate to heavy infections and is vulnerable to their impact on nutritional status.

Insert Table 3 here

Insert Table 4 here

Figure 2 shows the typical relationship between age and the prevalence of infection with *A.lumbricoides* derived from a study of people living in an urban slum in Bangladesh; a similar relationship is commonly observed for *T.trichiura*. Figure 2 indicates that infections are acquired in the first two years of life and that around 80% of all age classes are infected, a high but typical proportion.

Insert Figure 2 here

Hookworms tend to show a different pattern in which the prevalence typically increases with age, reaching a peak in late adolescence and adulthood (Bundy et al., 1992a). The reason for this difference is not clear, especially as children are less likely to wear shoes than adults and so could be considered to be more to be exposed to hookworm larvae on the soil. But

the differences in prevalence may reflect where worms are transmitted in what have been called “domains of infection” (Cairncross et al., 1996). The transmission of both *A.lumbricoides* and *T.trichiura* is thought to occur within or around the household, in the domestic domain, while hookworms may be transmitted beyond the household, in the public domain which is frequented more by adults than children (Cairncross et al., 1996).

Although the prevalence of infection in children may provide some indication of the importance of each worm in terms of health and nutrition, there is no clear threshold prevalence associated with disease, largely because the relationship between prevalence and the intensity of infection is strikingly non-linear. Figure 3 shows the relationship between the prevalence of infection with intestinal worms and the worm burden, derived from data collected in Bangladesh on *A.lumbricoides* (Hall et al., 1999). It can be seen that, below a prevalence of about 50%, the mean worm burden is relatively low, but rises almost exponentially above a prevalence of 60%. This means that even a prevalence of up to about 50% is associated with a low average worm burden, and that the prevalence of infection is a poor indicator of the probability of disease unless it is 70% or greater. This relationship helps to explain the use of a threshold prevalence of 50% for administering mass anthelmintic treatment for both soil-transmitted helminths and schistosomiasis, a threshold that was endorsed by a WHO Expert Committee in 2001 (WHO, 2002a). This threshold has subsequently been lowered by the WHO to 20% for mass treatment once a year in what they classify as “low risk” communities, and the WHO now apply the 50% threshold to define a “high risk” community where mass treatment twice a year is warranted (WHO, 2006).

Insert Figure 3 here

The relationship between prevalence and disease is further complicated by the mix of species: in many parts of the world it is common to find all three major types of worms together, so that some children have two or three infections. Although the prevalence of *A.lumbricoides* and *T.trichiura* is often correlated (Booth and Bundy, 1992), it seems that an infection with one species does not predispose to the presence of another. Figure 4 shows a diagrammatic representation of the percentage of individuals who have

multiple infections when the prevalence of *A.lumbricoides* is 60%, *T.trichiura* is 50% and the hookworms is 40%, all arbitrary but typical figures. If the probability of having one infection is independent of having another, then it can be estimated that 32% of individuals have at least two infections and 18% have all three infections (Figure 4).

There is no method to assess the impact of multiple infections: they could be additive but might be multiplicative or even antagonistic if species occur in the same location in the gut, such as *A.lumbricoides* and the hookworms. As multiple infections may be as common or more common than single infections, it is hard to estimate the relative benefit of treating each different species, especially as the drugs used to treat intestinal nematode worms are effective against all species, if to differing degrees (see Section 3.2).

In conclusion the WHO threshold of 50% infection provides a reasonable basis for applying mass treatment. Below this threshold few people have moderate to heavy worm burdens that cause disease and the majority are uninfected; above this threshold the likelihood of moderate to heavy infections increases exponentially. This is not to say that worms do not cause disease below a prevalence of 50%, but the effect on a very small minority may be lost in the group average. A prevalence of 50% was taken as a minimum for studies of deworming to be included in the meta-analysis reported below, and studies such as those of (Garg et al., 2002) in which the prevalence of infection with any worm before treatment with an anthelmintic was only 11%, were excluded. This threshold may seem somewhat arbitrary, but it is based on the relationship shown in Figure 3 and it would be unusual to include any uninfected individuals in a trial of a drug to treat a bacterial diseases. A prevalence of 50 – 100% represents a typical range in many human communities in which mass anthelmintic treatment is given, and the effectiveness of treatment in such studies represent common epidemiological circumstances.

2.3 Number and distribution of worms

Each worm that becomes established in a host represents the successful hatching, migration, establishment and development of a single fertile egg. Nematode worms do not multiply within their host, except for *Strongyloides stercoralis* (see above) the eggs of which can hatch within the lower bowel to release infective filariform larvae that penetrate the gut wall in a process called auto-infection (Schad, 1989). This explains the persistence of *S.stercoralis* in British soldiers who were prisoners of the Japanese in Asia during the second world war and who have developed strongyloidiasis in their old age (Gill and Bell, 1979, Gill and Bell, 1987, Gill et al., 2004).

For each of the four major types of intestinal worms the probability of disease is related to the number of worms in the host, called the worm burden. Figure 5 shows the average number of *A.lumbricoides* recovered from males in 11 age classes in an urban slum in Bangladesh who were given a drug that paralysed their worms so that they were expelled by peristalsis, then recovered, washed and counted. It shows that the heaviest average infections were found in school-age children from 5 – 15 years old, a characteristic typical of many helminth infections. The notable exception is the hookworms, for which the prevalence and mean worm burden tend to increase with age so that adolescents and adults tend to be most heavily infected (Bradley et al., 1992, Bundy, 1990).

Insert Figure 5 here

There are two theories to explain the shape of the distribution in Figure 5. First, it could reflect differences in behaviour, because children are more exposed to worm eggs than adults, perhaps as a result of playing on faecally contaminated ground and poor personal hygiene.

Second, it could reflect the development of a partially effective immune response to infection, or perhaps a more effective immune response in some individuals than others as a result of repeated exposure to worm larvae. The study in Bangladesh however found a statistically significant difference in the mean worm burden of *A.lumbricoides* between adult males (who leave their community to work during the day) and adult females (who stay at home in the crowded, unsanitary environment), which suggests that exposure more than immunity influences this distribution (Hall et al., 1999).

When the distribution of worms among hosts is examined it is typical to find that it is highly skewed, so that most individuals have light infections while a minority have moderate to heavy infections. Figure 6 illustrates this distribution using data on the number of *A.lumbricoides* recovered from 1,765 people who were treated with pyrantel pamoate to paralyse and expel their worms. The distribution shown in Figure 6 is best described by the negative binomial, which is purely an empirical fit, and implies nothing about the biological reason why worms should be distributed in this way. But this distribution, which is described as aggregated or over-dispersed, is typical of most helminth infections and has been observed even in pigs each of which have been infected experimentally with the same number of fertile eggs of *A.suum* (Boes et al., 1998, Stephenson et al., 1980a). This suggests that the distribution derives from differences between hosts in the establishment of worms rather than in differences in exposure to eggs.

Insert Figure 6 here

The equation that describes this distribution is defined by three parameters, the prevalence (P), the arithmetic mean worm burden (M), and by (k), a parameter that varies inversely with the degree of aggregation or clumping of worms in a few hosts so that:

$$P = (1 - (1 + Mk)^{-k}) * 100$$

The parameter k captures the degree to which worms in a small proportion of hosts tend to be aggregated, clumped or over-dispersed (terms commonly used in this context). Small values of k , typically less than 1, indicate a high degree of aggregation of worms, irrespective of age, sex or any other factor. The study in Bangladesh indicated that k varied with the mean worm burden so that, as the mean burden increased, the degree of aggregation decreased (Hall et al., 1999). The implication is that, when the average worm burden is large, more people are likely to have moderate to heavy infections and may be diseased as worms are less aggregated. Figure 7 shows the cumulative percentage of all worms recovered from 1,765 people in urban Dhaka plotted against the cumulative percentage of hosts, for worm burdens between zero and 187 worms. It shows that a half of all subjects expelled only 10% of all worms, and that 80% of all subjects contained only

40% of all worms. The remaining 60% of worms were recovered from only 20% of individuals.

Insert Figure 7 here

If it is typical to find that a small proportion of people harbour a large proportion of worms, what happens when they are treated? Evidence from studies of reinfection after treatment have found that heavily infected individuals tended to become heavily reinfected again while lightly infected people become lightly reinfected, leading to the theory that some individuals are predisposed to infection and others are not (Bundy and Cooper, 1988, Chan et al., 1994, Forrester et al., 1990, Haswell-Elkins et al., 1987, Holland et al., 1989, Kightlinger et al., 1995). If this is so, could efforts be concentrated on the individuals who were predisposed to worms? This was examined in a study of infection and reinfection with *A.lumbricoides* in 880 individuals in Bangladesh (Hall et al., 1992). It was found that, although there was evidence of a predisposition to moderate to heavy infections, over three rounds of treatment and two periods of reinfection of 6 months, about two thirds of all subjects were moderately or heavily infected at least once (Hall et al., 1992). This suggested that there was no benefit in identifying moderately to heavily infected people on the assumption that they were predisposed individuals, and mass treatment should be given rather than any form of selective treatment.

The biological implications of the aggregation of worms are that most individuals in a community at any one time have light infections, but a minority ranging from < 1 – 40% will have moderate to heavy infections and are most likely to be diseased. If treatment is given periodically and reinfection occurs (which will happen because eggs can persist in the environment for many months, if not years), then over a period of 2 – 3 years a majority of individuals will be moderately to heavily infected at some point. This has implications for measuring the impact of mass treatment, as a minority will benefit more than the majority in the short term, but over a longer period of periodic treatment, an increasingly larger proportion will benefit.

A light infection probably has little effect on the nutritional status of a host, and the worm burden is the key indicator of the probability of disease. This requires that worms are expelled and counted, something that is difficult

to do, and it destroys the worm burden at the same time, so that infected subjects can no longer be followed. So in most surveys of worms the concentration of eggs in faeces is used as an indicator of the intensity of infection. However the perception of egg counts tends to be relative, so that what is seen to be a moderate egg count in one place could be considered to be high or even low in another. To provide some guidance on assessing egg counts a WHO Expert Committee in 1987 suggested threshold egg counts to classify light, moderate and heavy infections with *A.lumbricoides* and *T.trichiura* (WHO, 1987). In 2002 a new Expert Committee added hookworm to the list although the previous committee had stated that egg counts for this worm could not be given because the “critical worm load differs locally depending on age, sex, iron intake and species of hookworm” (WHO, 2002a). These thresholds are shown in Table 5.

Insert Table 5 here

Since the Expert Meeting in 1987 it has been clearly shown for *A.lumbricoides* at least, that the relationship between worm burden and egg count is both non-linear and differs between worms in different countries (Hall and Holland, 2000). For example 20 worms was associated with around 1,300 eggs/g of faeces or 2,300 egg/g in two studies in Bangladesh, with 17,300 eggs/g in Iran, with 22,000 eggs/g in Nigeria and Madagascar, with 27,000 eggs/g in Burma, and with 44,500 eggs/g in Mexico (Hall and Holland, 2000). This indicates that there is no consistent relationship between egg counts and worm burdens that can be applied universally, for *A.lumbricoides* at least.

2.4 Duration of infection

One of the main factors besides the worm burden that is likely to contribute to the development of disease is the duration of infection, something that is not usually known. Table 6 shows the estimated life span of the major species of intestinal nematodes of humans.

Insert Table 6 here

But even if a worm such as *A.lumbricoides* can live for as long as two years and is then expelled from the gut when it dies, new worms are continually acquired so that people remain persistently infected with slowly

changing numbers of worms. Figure 2 indicates that just over 60% of children aged 1 – 2 years in the study in Bangladesh were infected with *A.lumbricoides* and Figure 5 indicates that they contained an average of about 7 worms. As both the prevalence and mean worm burden are higher in older age groups, it suggests that most people are infected throughout their life.

2.5 Rate of reinfection

If the population of worms in a community of hosts is perturbed by giving mass treatment with an anthelmintic, reinfection can occur immediately and the number of worms will rebound to a similar number as before, a state called equilibrium. Without treatment there may be fluctuations in time in the numbers of worms in individuals as some die and others are gained, but the number of worms in the community seems to reach a relatively steady state, perhaps driven by factors such as sanitation, the contamination of the environment, behaviours that put people at risk, and environmental conditions that favour the survival of infectious stages. Figure 8 shows the prevalence of infection with *A.lumbricoides* in 880 people at three rounds of treatment, six months apart and Figure 9 shows the mean worm burden on the same occasions (Hall et al., 1992).

Insert Figure 8 here

Insert Figure 9 here

The prevalence, shown in Figure 8, rebounded very quickly after treatments in the school-age children, perhaps because the force of infection was greater in this age class, but was lower at each round in the four adult age classes. The mean worm burden shown in Figure 9 was, however, lower at each round of treatment in all age classes except for the very youngest cohort, whose exposure to worm eggs probably increased as they became mobile and were increasingly exposed to worm eggs. Figures 8 and 9 show that periodic treatment may do little to perturb the prevalence of infection but, if given often enough, it can help to prevent reinfection with the same number of worms. In an environment such as an urban slum in Bangladesh, it may be necessary to give treatment for worms at least three times a year rather than twice annually, in order to sustain low worm burdens and reduce the probability of disease.

Figures 8 and 9 also illustrate that the prevalence is a poor indicator of the effectiveness of worm control by periodic deworming, and that an indicator of the intensity of infection is better (Bundy et al., 1992a). Ideally both should be measured during a programme of mass deworming.

2.6 Summary

The probability that an infected child has disease or malnutrition caused by intestinal worms is related to:

- The species of worm;
- The mixture of species;
- The worm burden of each species.
- And the duration of infection before treatment.

The number of worms is difficult to assess without expelling them from the gut. The concentration of eggs in faeces may only represent a worm burden in a specific locality, because fecundity varies with the number of worms and perhaps between strains of worms in different locations around the world. There are no threshold numbers of worms to classify burdens as light, moderate or heavy. There are no methods to combine the probability of disease due to different numbers of worms of different species in the same individual.

3. Factors affecting the impact of treatment

Section 2 has described how the biology of each species of worm and the distribution of worms among hosts is likely to influence the effect that they have on the growth and nutritional status of children. As it is unethical to infect children with worms and measure prospectively their impact on growth, evidence of the effect of worms on humans comes either from cross-sectional surveys or from experimental studies in which changes in key indicators of health, growth and nutrition are measured after giving treatment.

Cross-sectional studies are difficult to interpret. Although several have shown an association between infections with intestinal worms and undernutrition or stunted growth (Moore et al., 2001, Muniz et al., 2002, Al-

Mekhlafi et al., 2005, Gupta, 1990, Saldiva et al., 1999, Egger et al., 1990, Cerf et al., 1981), other studies have not (Pegelow et al., 1997) or have had mixed results (Mahendra Raj et al., 1997b). The best analysed studies have controlled for factors such as age, sex and socio-economic status, and have examined associations not just with the presence of infection, but with an estimate of the intensity of infection. The main problem with doing such analyses lies in the lack of data on the actual worm burden rather than on egg counts, which do not have a consistent relationship with worm burden, and with quantifying the combined effects of more than one species of worm.

There is also considerable potential for publication bias in cross-sectional studies because only interesting and biologically plausible associations are likely to be written up and submitted for publication, while negative findings are either not submitted or are less likely to be accepted by a scientific journal.

But the main scientific problem with cross-sectional studies is related to temporality: did malnutrition predispose children to infection with worms, or did worms cause the malnutrition? It is also unlikely that worms, and only worms, are responsible for all undernutrition or stunted growth. Worms are associated with poverty and a poor diet, so if worms have a harmful effect, it is likely to be in addition to underlying chronic malnutrition.

Second, infection with worms reflects exposure to human faeces, a waste material that contains many other pathogens in addition to worm eggs, such as viruses, bacteria and protozoa. Repeated episodes of diarrhoea and other infectious illnesses associated with living in an impoverished and unhygienic environment can also affect nutritional status through their effects on appetite, absorption and metabolic rate, as the studies of Mata and colleagues in Guatemala vividly demonstrated (Mata, 1978). Infection with worms is an indicator of life in an environment contaminated with human faeces.

These complexities mean that it is not adequate simply to compare the growth of a group of infected children after treatment with a control group who were not infected with worms (Mahendra Raj et al., 1997a, Mahendra Raj and Naing, 1998), nor is it adequate to explain the magnitude of weight gain after treatment in terms of prior egg counts (Stephenson et al., 1980b).

The need for untreated controls is reinforced when it comes to measuring the impact of treatment on weight gain or growth. Even when children are chronically undernourished, some growth can be achieved, so without a control group it is not possible to know whether a treatment has led to extra weight gain or extra growth over any given period. Making comparisons with a reference population to assess the degree of change in undernutrition will not provide an answer either. Even if an improvement in anthropometric indices is recorded, or a fall in the percentage of children who are in some way undernourished, such changes can occur as a result of secular improvements in food supply or a decrease in the transmission of other diseases such as malaria or diarrhoea over the period of a study.

This section describes factors that influence the impact of treatment on children's growth and nutritional status.

3.1 Study design: controls and randomisation

In order to estimate reliably the magnitude and statistical significance of the effect of a treatment on growth or nutritional outcome it is necessary to have an untreated control group (Stephenson, 1987). To ensure that naturally occurring differences between subjects are evenly distributed between groups before treatment is given, individuals also need to be randomly assigned to each study group. As there can be large differences between individuals in the intensity of infection because of the aggregated distribution of worms, if the sample size is small then subjects may need to be stratified first by egg count, before random allocation. If the sample size is large and the prevalence is high, then random allocation is likely to be sufficient.

If the treatments are allocated by clusters, such as villages or schools rather than to individuals, there must be a sufficient number of clusters to distribute any variation between clusters in the prevalence and intensity of infections evenly between study groups. Randomised cluster designs have the potential to provide the large sample sizes that are needed to be able to detect the effects of treatment on the minority of subjects who will benefit most from treatment.

Ideally all subjects in a control group in a simple randomised trial should be given an identical placebo. This is less easy to do in cluster

randomised trials, especially if anthelmintics are given through the health system. Effectiveness trials, such as the one done as a part of Child Health Fairs in Uganda (Alderman et al., 2006), typically have untreated controls, but they usually receive nothing rather than a placebo. This opens the study to potential bias because of self-treatment with anthelmintics among the control group.

3.2 Anthelmintic drugs and other treatments

The drugs used to treat infections with intestinal nematodes can be divided into two main types:

- Drugs that act on the nervous system to paralyse worms so that they are expelled from the gut by normal peristalsis, such as piperazine, levamisole and pyrantel pamoate;
- Drugs that inhibit metabolic processes, such as the benzimidazole derivatives albendazole, mebendazole and tiabendazole, which block the uptake of glucose by microtubules in the mitochondria of worms (Horton, 2002, Horton, 2000), and the relatively new treatment nitazoxanide, which acts in protozoa by inhibiting the enzyme pyruvate ferredoxin oxidoreductase (Esposito et al., 2005, Sisson et al., 2002, White, 2003).

There are differences between these types of drug in the efficacy with which they treat each species of intestinal worm (de Silva et al., 1997).

Efficacy is assessed in two ways:

- As the cure rate, which is the percentage of infected subjects in whose faeces worm eggs are no longer found after treatment (although some immature female or male worms could still remain, thereby over-estimating the cure rate);
- As the egg reduction rate, which is the percentage reduction in the arithmetic or geometric mean concentration of eggs in the faeces of infected individuals. The concentration of eggs reflects the number of female worms, and an even sex ratio is usually assumed.

The cure rate and egg reduction rate are typically estimated by collecting and examining under a microscope a faecal sample collected a few

days before treatment and then again some 14 – 21 days afterwards. The gap after treatment is advisable because there is evidence that the drugs may temporarily inhibit egg production by worms that have survived treatment (Hall and Nahar, 1994).

Because of their different modes of action the two types of anthelmintic drugs differ in their efficacy: drugs that paralyse worms tend to be less effective than those that inhibit metabolic processes, perhaps because the paralysis can wear off more quickly than the effects of a metabolic inhibitor, especially if worms are anchored to the gut wall. (If *A.lumbricoides* are expelled from the gut using a drug such as pyrantel or levamisole and placed in warm saline, they can recover their motility after a few hours, showing the transitory effect of the paralysis).

Table 7 gives a rough guide to the range in efficacy of each type of drug against the main species of intestinal nematode worms at the usual dosage given. Data are generally lacking for the drugs that paralyse worms, because they are older and less well studied than the highly effective benzimidazole drugs, mebendazole and albendazole, which superseded levamisole and pyrantel in 1975 and 1980 respectively (Horton, 2003b). In general the benzimidazoles are less effective against *T.trichiura* than against *A.lumbricoides* and the hookworms, and are less effective against hookworm than against *A.lumbricoides*.

Insert Table 7 here

There also seem to be differences in the efficacy of the two benzimidazole anthelmintics, even though they are chemically similar. Table 8 shows data from a large study in Zanzibar of treating intestinal nematode infections with albendazole or mebendazole which revealed statistically significant differences in the efficacy of treating hookworm (Albonico et al., 1994).

A reason for the lower efficacy of drugs to treat hookworm compared with *A.lumbricoides* may be because hookworms are usually physically attached to the gut and may be better able to resist the transient effects of anthelmintic drugs than *A.lumbricoides* which can only maintain their position in the gut by actively swimming against the intestinal flow.

The reason for the lower efficacy of *T.trichiura* compared with both *A.lumbricoides* and the hookworms may be because they live in the large intestine, where anthelmintic drugs may be more dilute than in the small intestine. Adult *T.trichiura* are also typically embedded in the gut wall by their whip-like anterior end, which may provide an anchor so that they, like hookworms, can withstand any transitory effects of anthelmintic drugs. A study in Bangladesh showed that, in order to achieve a cure rate for *T.trichiura* of 80%, 400 mg albendazole had to be given daily for three consecutive days (Hall and Nahar, 1994).

There is also evidence that there may be a lower cure rate for *T.trichiura* in Asia than in Africa: an analysis of trials of albendazole showed a median cure rate of 33% in Asia compared with 61% in Africa (Bennett, 2000),

There is obvious concern that repeated mass treatment could lead to the development of drug resistance, something that has been shown to develop as a result of repeated treatment (Albonico et al., 2003). There are substantial lessons to be learned from veterinary medicine in which the same anthelmintic drugs have been used for many years and far more intensively than in humans (Coles, 1995). Strategies to avoid or delay the development of drug resistance should be applied (WHO, 2002a), such as alternating drugs with different modes of action, and the efficacy of treatment should be assessed periodically at sentinel sites during mass treatment programmes, the interval to depend on the frequency of treatment (WHO, 2002a).

The main limitation to alternating treatments has been the lack of effective alternatives to the albendazole and mebendazole, as single dose treatments. One possibility is a combination of pyrantel and oxantel which has been shown to be quite effective in comparison with mebendazole (Albonico et al., 2002, Rim et al., 1975), but this mixture is not widely available. A combination of albendazole and ivermectin has been tested as a treatment for lymphatic filariasis (Beach et al., 1999b, Belizario et al., 2003, Horton et al., 2000) and has effects on the major species of soil-transmitted helminths as well. The advantage of giving two drugs in combination is that the chance of genes that confer resistance to both treatments at the same time is greatly reduced.

A relatively new drug called nitazoxanide has been shown to be an effective treatment for all major species of intestinal nematode worms as well as *Hymenolepis* spp (Juan et al., 2002, Romero Cabello et al., 1997). But the drug currently has to be given twice a day for three days whereas the others are single dose treatments, which ensures compliance in mass treatment campaigns. The major advantage of nitazoxanide is that it is an effective treatment for intestinal protozoa, including *Giardia duodenalis* and *Cryptosporidium* spp, as well as anaerobic bacteria such as *Helicobacter pylori* and *Clostridium difficile* (Bobak, 2006, Megraud et al., 1998). Such a drug could have a significant impact on growth and nutritional status, as studies of giving metronidazole, another broad-spectrum antibacterial and anti-protozoal drug have suggested (Gupta and Urrutia, 1982, Khin Maung et al., 1990).

The differences in the efficacy of treatments for intestinal nematode worms will therefore depend on the drug, the dose of drug, the species of worm, and the strain of the worm perhaps, which will all have consequences for the impact of treatment on nutritional status and growth. In some studies included in this review a single treatment was given, in others, repeated treatment was given using the same drug. And in one study included in the review, two different drugs were given: pyrantel pamoate at the first treatment and then mebendazole for subsequent bi-monthly treatments (Northrop-Clewes et al., 2001).

The situation is further complicated if anthelmintic drugs to treat other types of worms are given, such as praziquantel or metrifonate to treat infections with *Schistosoma* species. This is a genus of blood flukes found in Africa, the Middle East, Asia and South America, often concurrently with infections with intestinal nematode worms. *Schistosoma haematobium* causes bleeding into the urinary bladder as a result of the passage of the sharp-spined eggs through tissues, while the passage of the eggs of *Schistosoma mansoni* and *Schistosoma japonicum* through the gut wall also causes internal bleeding. Studies of the impact of treatment in areas in which schistosomes occur tend to give a drug to treat these infections, as well as a drug to treat intestinal nematode worms (Beasley et al., 1999, Friis et al., 2003). As well as treating schistosomes, the drug metrifonate is also an

effective treatment for hookworm (Kurz et al., 1986), which complicates studies and measuring outcomes due to treatment.

Finally, if any study is to assess the impact of treating intestinal worms alone, then additional treatments cannot be given unless a factorial design is used and an untreated control group is provided. One study of the effect of treating worms with mebendazole also gave all subjects metronidazole as well, a broad-spectrum anti-bacterial drug that also treats infections with intestinal protozoa (Marinho et al., 1991). This meant that the effect of mebendazole could not be separated from the effect of metronidazole. In other studies supplements of micronutrients or food were also provided which also may have had independent effects on nutritional status and growth so making it impossible to estimate the impact of deworming alone (Latham et al., 1990a, Lind et al., 2004, Majumdar et al., 2003).

3.3 Intervals between treatments

In an infected human population the death rate of worms tends to reach a balance with the rate at which worms are acquired, so an equilibrium develops. The effect of mass treatment is to cure a proportion of people, which reduces the prevalence of infection, and treatment expels a proportion of the total worm population, which reduces the mean worm burden. But, as there is no fully protective immunity to worms, reinfection can occur immediately, especially as infective eggs can survive in the environment for months in suitable conditions. The rate of reinfection is strongly related to the prior prevalence and mean worm burden, as well as to local sanitation, which influences the number of infective stages in the environment. Studies of reinfection after treatment and mathematical models that simulate treatment and reinfection have shown that the prevalence of infection can rebound within a few months after treatment, but that the worm burden takes considerably longer to reach the pre-existing number (Hall et al., 1992). This means that the prevalence may show only a small difference between rounds of treatment, but the mean worm burden may decline.

Figure 10 shows data on the prevalence of infection with *A.lumbricoides* among 445 school-age children in Bangladesh at the first treatment and after two more rounds of treatment, each six months apart.

The dotted line shows the trend which, when extrapolated, suggests only a small decline over two future rounds of treatment. Figure 10 also shows the mean worm burden at each round of treatment, which declines by almost 60% between the first and third treatment. If the linear decline was extrapolated it would lead to a substantial reduction in mean worm burden after five rounds of treatment. The relatively slow decline in worm burden achieved in the study in Bangladesh suggests that treatment would actually be best given every 3 – 4 months or 3 – 4 times a year rather than twice a year.

Insert Figure 10 here

Figure 10 makes the point that the interval between treatments will influence the average intensity of reinfection that occurs, assuming a high efficacy, especially in the absence of any measures to prevent exposure to infectious stages in the environment or if only a proportion of the population is treated. Ideally the intervals between treatment should prevent the prevalence rising above 50%, the threshold at which the probability of moderate to heavy infections begins to increase exponentially (see Figure 3).

The conclusion is that the frequency of treatment is therefore likely to affect the impact of treatment, and the aim should be to prevent moderate to large worm burdens from being reacquired. The consequence for this review is that it is difficult to compare studies of different numbers of treatments given over different periods. Nevertheless it can be useful to standardise gains in weight or any other parameter per unit of time, such as per year (Alderman et al., 2006). But, if reinfection is rapid, then two or even three treatments a year may have a greater impact than one, assuming that worms are the only constraint on growth.

3.4 Duration of follow up

It follows from the discussion in the previous section that, as well as the number of treatments given, the duration of follow up after treatment will affect the magnitude of any difference between a treated and an untreated control group, and therefore its statistical significance. This is illustrated in Figure 11 which shows hypothetical data on the weight of two cohorts of undernourished children, 300 treated and 300 untreated, over a period of three years during which the treated group were kept almost free of worms. The children were

five years old at the start of the study and were underweight, with an average body weight that was 2 standard deviations below the NCHS median. If the periodic treatment of worms led to an extra gain in weight of 0.5 kg a year, or 3.5% of the initial mean weight, then it can be seen from the confidence intervals around the means in Figure 11 that it is not until the third year that a statistically significant difference between groups is achieved

Insert Figure 11 here

The duration of follow up is important because, as Section 2.4 has shown, a relatively small proportion of infected subjects will benefit from treatment so it is likely to take some time before the effects of repeated treatment are detectable in comparison with an untreated infected group. Some studies have attempted to measure a difference between groups in weight gain or growth over a very short period, such as 3 or 7 weeks after treatment (Hadju et al., 1996). Even though there was a statistically significant difference between study groups in such studies, it is too short a period to warrant inclusion in the review. Another study attempted to measure a change in haemoglobin and iron status over a period of 10 days after treatment (Karyadi et al., 1996), which is also a very short time in which to expect an improvement.

3.5 Outcomes measured and the need for controls

The primary outcomes usually measured during studies of the effect of anthelmintic treatment are changes in body weight, height, mid upper arm circumference and skinfold thickness. A change in haemoglobin concentration may also be expected if hookworm or *T.trichiura* occur. Measuring vitamin A status is hard to do as the concentration of retinol in serum is usually sustained from liver stores, so some sort of dose response test is usually used. Secondary outcome measures are anthropometric indices such as height-for-age and weight-for-age, which both require age to be known, ideally to within a month, and weight-for-height or body mass index. Indices of weight-for-height can only be calculated for girls younger than 10 years and boys younger than 11.5 years if the National Centre for Health Statistics reference values are used (WHO, 1983) which may limit their application in studies of school-age children. Z-scores of anthropometric

indices are useful when controlling for the initial nutritional status of subjects based on the assumption that, when there is a large initial deficit, the impact of treatment is likely to be greater than if there is a small initial growth deficit. A change in z-score can also help to give a perspective to the magnitude and nutritional significance of an improvement.

It cannot be assumed that a gain in body weight is due totally to an increase in lean body mass, because some increase could result from the deposition of fat in adipose tissue. Although there are now available weighing scales that can estimate the percentage body fat by applying standard equations to measurements of electrical impedance, they cannot usually be applied to young children, and may not apply to undernourished children in a developing country either.

Measurements of mid-upper arm circumference and triceps skinfold thickness tend to be under-used in studies of child growth after deworming. Their value lies in the ability to estimate the surface area of sub-cutaneous fat and muscle in the arm, assuming a standard area of bone (Gibson, 1990) which could indicate both growth in lean tissue and the deposition of fat reserves.

A statistically significant weight gain can be achieved over a relatively short period, especially if food is available *ad libitum*, while a gain in height can take relatively longer. A period of about 12 weeks seems to be about the minimum period of follow up. A study of vitamin A and iron given to Tanzanian children after treatment with albendazole and praziquantel showed statistically significant extra gains in weight and height after 3 months of supplementation (Mwanri et al., 2000).

Studies of the effects of treating worms that cause blood loss require controls because the haemoglobin concentration can fluctuate naturally. Studies of giving iron supplements to school-age children after deworming have shown statistical significance only because the mean value of the control group may go down in comparison with the treated children whose haemoglobin was sustained by the iron (Hall et al., 2002, Roschnik et al., 2004, Aguayo, 2000). Natural fluctuations in haemoglobin may occur as a result of changes in the diet and diseases such as malaria, both of which may be seasonal.

3.6 Initial nutritional status

The impact of treatment on any indicator of nutritional status is likely to be related to the prior degree of undernutrition or deficiency, thus the margin for potential improvement. This was not the case in a study in South Africa of the effect of anthelmintic treatment and micronutrient fortified biscuits (Jinabhai et al., 2001b). One of the outcome measures was anthropometric status, but at the start of the study only 7.3% of children were stunted and 0.8% were underweight (Jinabhai et al., 2001b), not a large margin for improvement.

It may seem obvious, but it is also important that treatment and control groups should be similar before any treatment is given. A study of the impact of treatment with mebendazole given to young children as a part of an evaluation of the Integrated Management of Childhood Illness in western Kenya reported statistically significant differences in gains in weight, height and weight-for-age when infected and treated children were compared with infected and untreated controls (Garg et al., 2002). But in this study the treated children were significantly more undernourished than the control group: the z-score of weight-for-height of the group given the placebo was much greater than the treated children (Treatment -0.89 vs Control -0.19, $P < 0.001$) and there was a statistically significant difference in their initial weight-for-age as well (-1.43 vs -1.01, $P < 0.001$) (Garg et al., 2002). If the infected and treated children gained more weight it could easily have been because they started from a lower initial nutritional status and had a greater potential to achieve more catch-up growth. Both the treatment and control groups need to be similar if the impact of treatment on growth or most nutritional variables is to be compared reliably.

3.7 Age of subjects

The age of subjects will influence the measurement of the impact of anthelmintic treatment. This is because growth is not linear during childhood and shows two spurts, the first during the first two years of life, and the second during adolescence. Although the prevalence and intensity of worm infections tends not to be as high during the first two years of life as during the school-age years, the potential impact of worms early in life is greater, mainly because of the relative size of worms to their hosts, and the relative

magnitude of any extra weight gain achieved after treatment. An extra weight gain of 500 g over a year by a 5 year old girl whose weight is 2 S.D. below the mean is 3.6% of initial weight; for a 10 year old it is 2.3% and for a 15 year old it is 1.3%. Such an extra weight gain is of decreasing biological significance, unless it can be sustained each year, and will require a larger sample size to detect in the older age groups.

3.8 Remedial therapy after treatment

An implicit assumption of many randomised trials of anthelmintic treatment seems to be that removing worms will automatically lead to improvements in growth and nutritional status. This may happen, but only if the diet is adequate (Hall, 2007). If worms have impaired growth, the haemoglobin concentration or micronutrient status, their effects are most likely to have been due to the mechanisms outlined in Section 1.3 which are worth repeating here: by feeding on the host's food, secretions, tissues and blood; by causing maldigestion or malabsorption; by effects on appetite and food intake; and by causing responses to infection that consume or divert resources unnecessarily. The losses or deficits caused by worms cannot be rectified or remedied simply by removing the worms alone, although halting any pathological processes is an important first step. After worms have been killed the need is for remedial treatment of the underlying nutritional deficits by providing energy, protein and micronutrients, so that catch-up growth can be achieved. This is illustrated in Figure 12 and discussed in some detail in Section 6.2.

Ideally, children should be protected from moderate to heavy infections throughout their childhood by repeated treatment to keep worm burdens low, by primary measures such as sanitation to prevent faeces containing worm eggs from getting into the environment, and by secondary measures to prevent exposure to worm eggs, such personal hygiene.

Insert Figure 12 here

3.9 Summary

There are a number of factors related to anthelmintic drugs and study design that need to be considered when either designing studies or evaluating papers that report studies.

- Different drugs give a different cure rate and egg reduction rate for each species of intestinal nematode;
- All anthelmintics are highly effective against *A.lumbricoides*;
- Albendazole 400 mg and mebendazole 500 mg are the best treatments available for hookworms and *T.trichiura*;
- At these dosages albendazole is more effective than mebendazole against hookworm infections, but both achieve egg reduction rates of 55 – 95%;
- Neither albendazole nor mebendazole given as a single dose cures many infections with *T.trichiura*, but such treatment can reduce egg counts by 50%
- Albendazole and mebendazole may be a less effective treatment for *T.trichiura* in Asia than in Africa
- Three daily doses of albendazole or mebendazole may be needed to achieve high cure rates for *T.trichiura*.
- Reinfection with worms can occur immediately after treatment, so treatment needs to be given periodically.
- The interval between treatments may influence the impact on growth and nutritional status.
- The subjects for study should be malnourished as well as infected.
- As a minority of children (ranging from 10 – 40%) have moderate to heavy infections, not all will benefit to the same degree from treatment, and the impact on the average will of any outcome measure may be diluted.
- These factors should be taken into account so that the period of follow up after treatment should be sufficient to be able to detect a statistically significant effect.

- It cannot be expected that nutritional status will improve and show catch-up if the diet of subjects is inadequate to meet the extra requirements.

4. Aims and methods of the meta-analysis

The aim of the review was to identify studies that had measured the effect of anthelmintic treatment given for infections with *A.lumbricoides*, *T.trichiura* and both species of hookworm on children's growth and weight gain, or on haemoglobin concentration.

4.1 Search terms

Table 9 shows the terms used in combination to search Medline. The search was limited to papers on humans in the following groups: infant, preschool, child and adolescent. Only papers in English were located. In addition, the reference list of each paper identified was scanned for other papers, so too was the Cochrane Review of 2000 (Dickson R, 2005, Dickson et al., 2000a, Dickson et al., 2005) and the book by Stephenson (1987) *Impact of helminth infections on human nutrition* (Stephenson, 1987). One unpublished paper known to the principal author, who was a co-investigator, was included (Partnership for Child Development, 2001).

All papers identified were summarised under the following headings:

- Design. A summary of the study design, including whether placebo controlled and blinded or not.
- Follow-up. The period children were studied after treatment, or the difference in time between the initial, interim and final measurements.
- Location. The region and country where the study was done.
- Age range.
- Infection prevalence at baseline. The prevalence of each species of worm recorded.
- Treatments. The drugs used and the doses given.
- Sample size. The number of subjects studied in each group.
- Outcomes. The principal outcome measures and any derived indices.

- Findings. A summary of the major findings with standard deviations and the statistical significance of any differences between groups.
- Notes. A summary of the prevalence of each intestinal nematode infection; a summary of the effect of treatment of worms; a summary of the degree of undernutrition estimated as z-scores, the mean haemoglobin concentration or the prevalence of anaemia; and short notes on other major or different features of the study.
- In Cochrane review of 2000 (recorded as Yes or No):
Dickson R, Awasthi S, Demellweek C, Williamson P. *Anthelmintic drugs for treating worms in children: effects on growth and cognitive performance (Review)*. Cochrane Database of Systematic Reviews, 2000, Issue 2. DOI: 10.1002/14651858.CD000371.
 - Included in meta-analysis. Either Yes, or the reason the study was excluded is given.

4.2 Inclusion criteria

Papers were included in the analysis if the following criteria were met:

- Studies of treating children and adolescents (aged 1 – 19 years) for intestinal nematode worm infections with albendazole, levamisole, mebendazole, piperazine or pyrantel (pamoate or embonate).
- An experimental group given the anthelmintic alone.
- An untreated control group.
- Random allocation to treatment and control groups.
- An initial prevalence of infection in children in the study locality with any species of intestinal nematode worm of $\geq 50\%$, the threshold used by the WHO to classify a “high risk” community (WHO, 2006).
- A duration of follow-up of at least 12 weeks for all outcomes except the modified relative dose response test to an oral dose of retinol (Tanumihardjo et al., 1996a).
- Outcomes measured included at least one primary outcome variable among weight, height, mid upper arm circumference, skinfold thickness, haemoglobin concentration, and a measure of serum retinol;

or secondary outcomes based on weight-for-age, height-for-age or weight-for-height such as z-scores or percentages of the median.

- Data given as a mean with standard deviation and sample size, or enough data to calculate the standard deviation.

Data from the study of (Koroma et al., 1996) were entered separately for urban and rural children.

4.3 Exclusion criteria

Papers were excluded from the meta-analysis for one or more of the following reasons (the references cited are examples, and is not a comprehensive list):

- Data on an outcome measurement not presented in a form that could be used e.g. change in percentage weight for height (Hadidjaja et al., 1998), difference in percentage improved (Kloetzel et al., 1982), change in percentage with anthropometric indices less than -2 z-scores (Lai et al., 1995), weight gain presented as a graph (Sur et al., 2005), no data given for stated outcome measures for treated children (Olds et al., 1999); or data are unique so could not be combined with other studies (Tanumihardjo et al., 1996b).
- No standard deviations of outcome measures given (Beach et al., 1999a, Fox et al., 2005, Greenberg et al., 1981, Michaelsen, 1985, Rousham and Mascie-Taylor, 1994, Willett et al., 1979) so not amenable to meta-analysis using Review Manager 4.2 software.
- The initial prevalence of worms was less than the “high risk” threshold of 50% (Garg et al., 2002, Awasthi et al., 2000, Awasthi and Pande, 2001, Donnen et al., 1998, Freij et al., 1979);
- Inadequate control group or method of allocation e.g. infected subjects treated and compared with subjects who were lightly infected or uninfected (Mahendra Raj and Naing, 1998, Mahendra Raj, 1998, Bhargava et al., 2003, Callender et al., 1994); a sample size of two, one village where children were treated and another control village where they were not (Fernando et al., 1983); or no untreated controls (Forrester et al., 1998).

- Treatment given for other conditions in addition to treatment for intestinal nematode worms e.g. metrifonate, which treats hookworm as well as *Schistosoma* spp (Stephenson et al., 1989a, Stephenson et al., 1989b, Stephenson et al., 1985); praziquantel to treat *Schistosoma* spp combined with a drug to treat intestinal nematode worms (Beasley et al., 1999, Kruger et al., 1996, Jalal et al., 1998, Jinabhai et al., 2001a); or food or micronutrient supplements given in addition to anthelmintic treatment (Cerf et al., 1981, Marinho et al., 1991, Jinabhai et al., 2001b, Mwaniki et al., 2002, Kruger et al., 1996, Palupi et al., 1997)
- Short period of follow up e.g. 3 and 7 weeks (Hadju et al., 1996), 10 days (Karyadi et al., 1996).

4.4 Meta-analysis

Data from suitable papers were extracted and entered manually into RevMan version 4.2.8 for Windows.^b

Statistical comparisons were made between subjects treated with an anthelmintic drug and untreated controls for the outcomes listed in Table 13. For some studies the standard deviations had to be calculated from 95% confidence intervals and the sample size. For studies in which the mean and standard deviations of values before and after were given, the difference between mean values was used in the analysis with a pooled estimate of the standard deviation.

The weighted mean difference between treatment and control groups was calculated with 95% confidence intervals in RevMan 4.2 software (RevMan, 2003) for each variable using a fixed effects model. Studies were disaggregated into sub-categories by treatment except that studies in which mebendazole and albendazole were given were combined, as the two drugs are chemically similar and have the same mode of action.

^b Downloaded from <http://www.cc-ims.net/RevMan>

5. Results of the meta-analysis

A total of 58 published papers were found, summaries of which can be found in the Appendix. They were not all unique studies as some data were reported in more than one paper. A total of 40 papers were not included in the analysis either because they met exclusion criteria or did not meet inclusion criteria; this left 18 studies for analysis. One additional unpublished study, a randomised cluster trial of albendazole in Vietnamese schoolchildren, was included, (Partnership for Child Development, 2001) increasing the sample to 19 papers, as follows:

Adams *et al.* (1994). Physical activity and growth of Kenyan school children with hookworm, *Trichuris trichiura* and *Ascaris lumbricoides* infections are improved after treatment with albendazole. *Journal of Nutrition* **124**: 1199 – 1206. (Adams *et al.*, 1994)

Alderman *et al.* (2006) Effect on weight gain of routinely giving albendazole to preschool children during child health days in Uganda: cluster randomized controlled trial. *British Medical Journal* 333: 122 -24. (Alderman *et al.*, 2006)

Dossa *et al.* (2001). Impact of iron supplementation and deworming on growth performance in preschool Beninese children. *European Journal of Clinical Nutrition* 55: 223 – 228. (Dossa *et al.*, 2001)

Gupta *et al.* (1982). Effect of periodic anti-*Ascaris* and anti-*Giardia* treatment on nutritional status of preschool children. *American Journal of Clinical Nutrition* 36: 79 – 86. (Gupta and Urrutia, 1982)

Koroma *et al.* (1996). Effects of albendazole on growth of primary school children and the prevalence and intensity of soil-transmitted helminths in Sierra Leone. *Journal of Tropical Pediatrics* 42: 371 – 372. (Koroma *et al.*, 1996)

Northrop-Clewes *et al.* (2001). Anthelmintic treatment of rural Bangladeshi children: effect on host physiology, growth, and biochemical status. *American Journal of Clinical Nutrition* 73: 53–60. (Northrop-Clewes *et al.*, 2001)

Partnership for Child Development (2002, unpublished). A randomised cluster trial of six-monthly deworming and its effects on the growth and

- educational achievements of Vietnamese school children. (Partnership for Child Development, 2001)
- Sarkar et al. (2002). Effect of deworming on nutritional status of *Ascaris* infested slum children of Dhaka, Bangladesh. *Indian Pediatrics* 39: 1021 – 1026. (Sarker et al., 2002)
- Simeon et al. (1995). Treatment of *Trichuris trichiura* infections improves growth, spelling scores and school attendance in some children. *Journal of Nutrition* 125: 1875 – 1883, (Simeon et al., 1995)
- Stephenson et al. (1989c). Treatment with a single dose of albendazole improves growth of Kenyan schoolchildren with hookworm, *Trichuris trichiura* and *Ascaris lumbricoides* infections. *American Journal of Tropical Medicine and Hygiene* 41: 78 – 87.(Stephenson et al., 1989c)
- Stephenson et al. (1993a). Weight gain of Kenyan school children infected with hookworm, *Trichuris trichiura* and *Ascaris lumbricoides* is improved following once- or twice-yearly treatment with albendazole. *Journal of Nutrition* 123: 656 – 665. (Stephenson et al., 1993b)
- Stephenson et al. (1993b). Physical fitness, growth and appetite of Kenyan school boys with hookworm, *Trichuris trichiura* and *Ascaris lumbricoides* infections are improved four months after a single dose of albendazole. *Journal of Nutrition* 123: 1036 – 1046. (Stephenson et al., 1993a)
- Stoltzfus et al. (1997). School-based deworming program yields small improvement in growth of Zanzibari school children after one year. *Journal of Nutrition* 127: 2187 – 2193. (Stoltzfus et al., 1997)
- Stoltzfus et al. (1998). Effects of the Zanzibar school-based deworming program on iron status of children. *American Journal of Clinical Nutrition* 127: 179 -186. (Stoltzfus et al., 1998)
- Stoltzfus et al. (2004). Low dose daily iron supplementation improves iron status and appetite but not anemia, whereas quarterly anthelmintic treatment improves growth, appetite and anemia in Zanzibari preschool children. *Journal of Nutrition* 134: 348 – 356. (Stoltzfus et al., 2004)
- Tanumihardjo et al. (1996) Vitamin A status of Indonesian children infected with *Ascaris lumbricoides* after dosing with vitamin A supplements and

albendazole. Journal of Nutrition 126: 451 – 457.(Tanumihardjo et al., 1996b)

Tanumihardjo et al. (2004). Vitamin A status and hemoglobin concentrations are improved in Indonesian children with vitamin A and deworming treatments. European Journal of Clinical Nutrition 58: 1223 – 1230. (Tanumihardjo and Permaesih, 2004)

Thein-Hlaing et al. (1991). A controlled chemotherapeutic intervention trial on the relationship between *Ascaris lumbricoides* infection and malnutrition in children. Transactions of the Royal Society of Tropical Medicine and Hygiene 85: 523 – 528. (Thein-Hlaing et al., 1991)

Watkins et al. (1996). Effect of removing *Ascaris* on the growth of Guatemalan schoolchildren. Pediatrics 97: 871 -876.(Watkins and Pollitt, 1996)

Table 10 shows a summary of the key features of the 19 studies. The studies could not be disaggregated by age into pre-school (1 – 5 y) and school age (6 – 15 y) because several had overlapping age ranges, particularly the largest study, undertaken by Alderman *et al.* (Alderman et al., 2006) in Uganda.

Insert Table 10 here

5.1 Geographic origin of studies

Table 11 shows the countries represented in the papers found and used in this review. Of all 58 papers found, nearly 50% reported data from Africa. Of the 19 papers used in the analysis, a little more than 50% reported data from Africa.

Insert Table 11 here

5.2 Estimates of effects

Table 12 presents summary data on the impact of treatment on 12 variables for all studies in which intestinal worms were treated with any effective anthelmintic. The drugs used were albendazole and mebendazole, levamisole, piperazine or pyrantel pamoate. There were statistically significant differences for most variables related to growth; neither of the outcomes for micronutrients were statistically significant.

Insert Table 12 here

Table 13 presents summary data on the impact of treatment on 12 variables for all studies in which intestinal worms were treated with albendazole or mebendazole only, as these drugs are now the most widely used and most broadly effective anthelmintics.

Insert Table 13 here

5.3 The figures and how to interpret them

Figures 13 to 24 show the mean differences between treated and control groups for each study grouped vertically by the drugs used. The mean is shown as a box around the vertical line of zero difference, with 95% confidence intervals (95% CI) shown as bars. The diamonds represent the weighted mean difference (WMD) between the treated and control groups for each treatment group and in total. The percentage weight given to each study is shown and the numerical value of the estimated difference with 95% CI. It should be noted that the scale in all but figures except for Fig 22, 25 and 25 is from -4 (favours control) to 4 (favours treatment).

5.4 Sources of error or bias

The decision to exclude studies in which the initial prevalence of infection is < 50% is somewhat arbitrary, but is based on the WHO threshold which classifies them as “low risk” communities (WHO, 2006). Ideally all children taking part in studies of anthelmintic treatment would be infected with at least one species of worm, just as any drug trial would be conducted only on infected individuals. But most trials of the impact of anthelmintics on child growth tend to study groups of children rather than infected subjects only, so tend to be trials of effectiveness rather than efficacy. This type of study is driven also because of ethical problems with having infected but untreated children as controls, so studies tend to be done in communities in which the prevalence is known, and whether individual subjects are infected or usually unknown. Applying a threshold prevalence of 50% or more means that a half of all subjects or fewer will not benefit from anthelmintic treatment, and their inclusion in the study sample will to some degree dilute the impact of treatment on the infected majority. The threshold prevalence of 50% does not

serve to maximise the impact of treatment, a prevalence of 100% is needed to do that, but a prevalence higher than 50% serves to reduce the effect of uninfected subjects. This means that the conclusions of the meta-analysis can only be applied to circumstances in which the prevalence is more 50% and excludes what the WHO calls “low risk” communities, in which the prevalence of infection with any species of worm lies between 20 – 49% (WHO, 2006).

About a half of all papers found and used in the analysis reported data from Africa. All of the papers reporting African data were from sub-Saharan Africa, reflecting concern for the effects of worms in African children.

In many parts of sub-Saharan Africa children are concurrently infected with species of *Schistosoma*, which may cause loss of appetite, internal bleeding, and tissue damage and inflammation due to reactions to the eggs of worms when they become lodged in tissues. Studies were excluded from this analysis in which subjects were also treated with praziquantel or metrifonate, the drugs most commonly used to treat *Schistosoma* spp, as this would over-estimate the effect of treating intestinal nematodes. This could, however, have led to a bias against studies from sub-Saharan Africa. But this did not seem to be the case, as a larger proportion of all papers from Africa were included in the final analysis than in Africa, Asia or the Indian sub-continent. Of the papers found and the papers used, the proportion from Africa was similar in both categories (28/59 or 47% and 11/24 or 46%).

Insert Figures 13 to 24 here

6. Discussion

This meta-analysis indicates that if the prevalence of intestinal nematodes is 50% or more then giving anthelmintic drugs leads to significant extra gains in weight, height, mid upper arm circumference and skinfold thickness in comparison with untreated controls. Table 12 shows the weighted average changes recorded in the studies found. The gains in weight and height also led to improvements in indices of anthropometric status in studies in which only these outcomes were reported. There was no evidence of a significant effect of treating intestinal nematode infections on haemoglobin concentration. Only two studies, both by the same author in Indonesia, were reported of the dehydroretinol to retinol ratio, and found no difference between treated and control groups (Tanumihardjo and Permaesih, 2004, Tanumihardjo et al., 1996b).

6.1 Magnitude of effects

It is not possible to say anything conclusive about the absolute magnitude of any effects of giving treatment, for a number of reasons. The studies summarised were different in terms of:

- the species and mixture of species of worms;
- the distribution of worms between hosts;
- the drug and dose used, leading to variability in the efficacy of each treatment;
- the number of treatments given and intervals between them;
- the initial degree of undernutrition, the age and current health of subjects;
- and the period of follow-up after treatment, or the gap between the initial and final measurements.

The magnitude of the extra increases shown in Figures 14 – 25 are not standardised as gains per unit time, which would have enabled them to be better compared, and would have put any improvement into some sort of perspective. A extra gain in weight of 0.2 kg in four months is much bigger and more significant in terms of growth than a extra gain of 0.2 kg over a year. Any gain per unit time will also be influenced by the frequency of treatment,

thereby keeping worm burdens down, perhaps. This was indicated in the study in Uganda: children who were dewormed at least every six months gained an extra 10% in weight compared with the 5% extra by children who were treated only annually (Alderman et al., 2006). However this could have been confounded by the fact that other health services were delivered at the Parish Health Fairs to children who came more often, or perhaps the regular attendance of children at Health Fairs also reflected better care at home.

If the magnitude of any gain is related to the initial degree of undernutrition, then it might be better to standardise the gain per unit time as a proportion of the initial value, though this may be statistically difficult to do. This could be important for the haemoglobin concentration. For example, an increase of 10 g/L when the initial average was 90g/L (11%) is more significant than an increase of 10 g/L when the initial average was 110 g/L (9%).

Nothing can be said about whether any particular drug is more effective than another at bringing about an improvement in a nutritional outcome, although egg reduction rate is likely to be a good indicator of this. The benzimidazole drugs are currently the most efficacious treatments available for treating intestinal nematode worms. Albendazole was the most commonly used drug (Table 10), and is effective to differing degrees against the three main species of worms, as Table 7 shows. Mebendazole has a similar efficacy but was given less often, probably because it used to be given as a dose of 100 mg a day for 3 days rather than as a single dose of 500 mg, as it is now used. A single dose of an effective drug is a crucially important attribute for a helminth disease control programme. However neither albendazole nor mebendazole are highly effective against *T.trichiura* (Bennett, 2000), and a failure to achieve a good egg reduction rate could contribute to a smaller impact of treatment than could be achieved by giving multiple doses.

6.2 Treatment alone is not enough

Whatever extra gains in nutritional or anthropometric outcomes are achieved after treatment with an anthelmintic drug, they do not occur solely as a result of that treatment. Catch-up growth, for example, requires extra nutrients and energy, and if they are not available after treatment then growth rates are

likely to remain unchanged. Alternatively a statistically significant difference between a treatment and control group could occur during a study because an untreated control group remain persistently diseased as a result of their infections, and thus gain less weight than the treated group.

The lack of extra food to meet the needs for growth could explain the lack of impact of deworming in many studies, such as the large cluster trial in Viet Nam (Partnership for Child Development, 2001). The expulsion of worms from the gut may remove a constraint that acts through effects on appetite and food intake, digestion and absorption, or because of the diversion of nutrients in response to infection. But to achieve the maximum growth rate after treatment, energy, protein and micronutrients need to be provided to children, preferably *ad libitum*. Most studies did not give food supplements after treatment, but one that did showed an improved appetite measured as food intake as well as improved growth (Stephenson et al., 1993a).

Catch-up growth is possible (Golden, 1994) especially if the deficits occur early in childhood and are treated adequately. Studies of children treated for *Trichuris* dysentery syndrome, admittedly an acute disease, have shown an average gain of nearly 11 cm in height and 4 kg in weight a year, which was more than 2 S.D. above the expected gain in height and weight of British children of the same age (Cooper et al., 1995). Some of the 5-year-old children studied showed an annual growth velocity of nearly 20 cm a year and a weight gain of 10 kg.

To achieve such catch-up growth children need to be fed *ad libitum*, not just with energy and protein, but also with micronutrients, so that no nutrient is limiting and the maximum possible growth is achieved (Hall, 2007). If studies of deworming have failed to show an impact on growth or weight gain it could be because children were not getting enough of the food and micronutrients they needed to achieve catch-up growth. And the studies that have shown a statistically significant impact of treatment may have underestimated the potential effect if children did not have an ideal and balanced diet given *ad libitum*. No published studies have been found of randomised controlled trials of deworming with or without any form of remedial feeding given *ad libitum*; most studies have only given supplementary food or supplementary micronutrients.

A problem with giving food supplements is that there can be substitution, in which people eat less food at home after being fed at school or work (Wolgemuth et al., 1982). Or supplementary food may benefit the better off most: a study of a school nutrition programme in Viet Nam found that better nourished children gained more weight than undernourished children (Hall et al., 2007), which is not what is hoped for in school feeding programmes.

The need for adequate remedial treatment is important when the outcome being measured is the haemoglobin concentration. A study in Tanzania of giving iron supplements to anaemic children after treating their infections with hookworm and *Schistosoma haematobium* showed no improvement in the mean haemoglobin concentration, but the serum ferritin concentration increased, an indicator of improved iron status (Beasley et al., 2000). This suggests that iron was not the micronutrient limiting the haemoglobin concentration.

This does not mean that improvements in growth and nutritional status cannot be achieved by deworming alone, especially if there are improvements in appetite and food is available to children. But to have the maximum effect on growth and nutritional status, therapeutic nutrients are needed as well. A failure to have an impact could be because of this lack, or because the worms were not an important cause of any nutritional deficit in the first place.

But the costs of only giving supplementary food can be quite high: the World Food Programme estimate that it costs \$34 a year to feed a child in school (World_Food_Programme, 2006). An alternative is to provide micronutrient supplements, a deficiency of which may also act to impair growth, and which have been shown to reduce the intensity of reinfection with schistosomes (Olsen et al., 2003). A multiple micronutrient supplement is a much less expensive intervention than food, and may cost only around one US cent/child/day if purchased in large quantities. But the key point is that if any nutrient is not provided in sufficient amounts to meet demands, and becomes rate limiting, then growth after deworming may be constrained.

The weighted average gains in parameters of growth shown in Table 12 therefore do not indicate what extra growth might be achieved after treatment or indicate the potential for growth, they only estimate what can be

achieved after giving treatment. If a study included in the analysis showed no statistically significant difference between the treatment and control groups, the question is: did this happen because there was no effect, or because treated children were lacking sufficient energy or nutrients to show extra growth and weight gain? A lack of effect in such studies will serve to reduce the weighted average, and so underestimate the potential impact of treatment. It is also entirely possible that anthelmintic treatment may have had no effect even if children had been adequately nourished. But, as there are plausible biological mechanisms by which moderate to heavy burdens of worms can affect nutritional status, a beneficial impact on some (but not all) children seems likely.

This touches upon the aggregated distribution of worms and the uneven distribution of the impact of treatment. If disease and malnutrition are a consequence of moderate to heavy infections, then in any given sample of children a minority will benefit most from treatment, so the effect of treatment will not be evenly distributed between children. For example if 25 - 49 *A.lumbricoides* is arbitrarily considered to be a moderate infection in children and 50 or more worms is a heavy infection, then of the 1,069 children aged 1 – 14 years studied in an urban slum in Bangladesh, 18% were moderately heavily infected and 7% heavily infected (data from (Hall et al., 1999)). If only these children benefited from treatment then the impact on this 25% would in effect be diluted in the lack of change in the remaining 75%. The average treatment effect therefore includes a large proportion of children who would not be expected to benefit, and would under-estimate the potential impact on moderately to heavily infected children. The proportion of lightly infected children will be very large when the prevalence is low, and when it is less than 50% it might be expected that very few children would benefit substantially from treatment. The general consequence is that the study average will not capture the larger benefit experienced by any moderately to heavily infected children.

One way to control for this would be to analyse the relationship between any outcome and an estimate of the intensity of infection, such as the concentration of eggs in faeces. This method was used by (Stephenson et al., 1993a) in their studies of the effect of anthelmintic treatment on

appetite. This can only be done if a prior individual diagnosis is made and, if it is, it could be considered to be unethical to leave children untreated whose infections have been diagnosed. One way to deal with this dilemma is to randomly allocate subjects to treatment and control groups but only diagnose infections in the subjects who will be treated. This was done in a study in Tanzania in which in which infections were diagnosed in the control group at the end of the study (Bhargava et al., 2003). The problem with doing this is that the intensity of infections can change in the control group as worms are lost or gained during a long study, so the treatment and control groups cannot be compared at any point during the study.

Two assumptions are commonly made about the effect of the intensity of infection, First, that treatment has an impact only above a threshold worm burden, which seems reasonable, though the threshold number is likely to be dependent on factors such as the size and current health of the host. Second, that above the threshold the impact of treatment on more heavily infected individuals is linear. This may not be the case, but is very difficult to assess without having heavily infected children as controls during a study, something that would be unethical. An alternative is to examine the nature of the relationship between the intensity of infection with a worm and an outcome that is easily measurable, such as hookworm and haemoglobin concentration. Cross-sectional studies typically find a non-linear relationship so that the subjects with the heaviest infections have a markedly lower haemoglobin concentration than lightly infected individuals (Lwambo et al., 1992, Pritchard et al., 1991, Srinivasan et al., 1987, Roche and Layrisse, 1966).

This meta-analysis found no statistically significant effect of treating intestinal nematode worms on the mean haemoglobin concentration of children (Tables 8 and 9). Yet the potential impact of treating worms that cause internal bleeding, dysentery and the loss of iron, is large. In Africa in particular, many children are infected with species of *Schistosoma* in addition to hookworms, which makes it difficult to assess the impact of treating the intestinal nematodes alone. An important study in Tanzania showed that supplements of vitamin A and iron are needed if rapid improvements in haemoglobin concentration are to be achieved after deworming (Mwanri et al., 2000). All children in the study were given albendazole and praziquantel,

then were divided into four groups to receive on 3 school days a week either iron and vitamin A placebo, vitamin A and an iron placebo, iron plus vitamin A, or iron and vitamin A placebos (Mwanri et al., 2000). The haemoglobin concentration of children given both placebos rose by an average of only 3.6 g/L in the 12 weeks after treatment which might have been a statistically significant increase, but there was no untreated control group to allow this to be assessed. The effects of the supplements of iron and vitamin A were partially additive and achieved an increase in haemoglobin concentration of 22 g/L over the same period compared with 13.5 g/L for vitamin A alone and 17.5 g/L for iron alone. This study illustrates the importance of giving micronutrient supplements after treatment in order to achieve a rapid increase in haemoglobin concentration and may explain why no statistically significant effect of anthelmintic treatment alone was detected in the meta-analysis. If the change of 3.6 g/L over 12 weeks in the control group reflects the effect of anthelmintic treatment alone, then it might have taken six times as long to achieve an increase of 22 g/L, or nearly a year and a half. The inclusion of vitamin A in addition to iron makes the important point that not all anaemia is iron deficiency anaemia, and this could explain the results of a study in Tanzania that gave iron alone and failed to achieve an statistically significant increase in haemoglobin concentration (Beasley et al., 2000).

6.3 The Cochrane Collaboration Review

The Cochrane Collaboration supported a meta-analysis in 2000 (Dickson et al., 2000a, Dickson et al., 2000b). The reviewers noted heterogeneity between the results of the trials they included, and considered that they could be due to a number of factors. These were: the prevalence and intensity of infection, so that only heavily infected children benefited from treatment; the site of the study (school, community or health facility); the age of children; the prior nutritional status of children; and the manufacturer of the drug. The reviewers concluded that “there is some limited evidence that routine treatment of children in areas where helminths are common has effects on weight gain, but this is not consistent between trials”. The heterogeneity noted by the Cochrane Review really means a lack of effect in some trials which could be due, as explained here, to the fact that anthelmintic treatment

alone is not sufficient to achieve improved nutritional outcomes. The review received considerable criticism concerning the methods of analysis and conclusions (Bhargava, 2000, Michael, 2000, Cooper, 2000, Savioli et al., 2000, Bundy and Peto, 2000).

This review was withdrawn in 2007 and replaced by a new analysis that examined effects on growth and school performance (Taylor-Robinson et al., 2007). The review drew similar conclusions: deworming may lead to improved weight gain in some circumstances but not others, and no effect on cognition or school performance has been demonstrated (Taylor-Robinson et al., 2007).

6.4 Characteristics of an ideal study

Any studies that attempt to estimate the effect of anthelmintic treatment plus any supplement should ideally have a factorial design. This is illustrated in Figure 25 in which four groups of subjects are given either deworming or not with a nutritional intervention or not, though it could be applied to any treatment. The factorial design is powerful, but requires randomisation of subjects to study groups and an untreated control group to allow the effect of secular change to be estimated and subtracted from the effect of treatment.

Insert Figure 25 here

However it is important to appreciate that it may be possible to bring about an improvement in a nutritional variable by a nutritional intervention alone, so that the effect of deworming will be masked. An analogy of a leaking bucket of water may be helpful to explain this concept. The level of water in a bucket, which is the measured outcome, can be sustained or even raised if the water flowing into the bucket is greater than the loss through any leaks. Simply plugging the leaks will not raise the water level, it is necessary to add more water to achieve this. But adding water alone could overcome or mask the effect of the leaks and lead to a rise in the water level. Once the bucket is full, the excess simply overflows but the leaks continue. This creates a paradox: once you start to fill the bucket the change in the level of water no longer accurately reflects the leakage that is occurring.

This analogy may apply better to anaemia than to body weight, as the concentration of haemoglobin does not rise unchecked, although some

excess nutrients such as iron and vitamin A can be stored. When worms cause a loss of blood and iron and the haemoglobin concentration falls, it will do so when all stores of iron needed to make haemoglobin have been used up (Crompton and Whitehead, 1993). Treating hookworms will not lead to an increase in the haemoglobin concentration if the diet does not contain enough nutrients to supply normal turnover, which is estimated to be about 0.8% of all red blood corpuscles daily, and to provide for increased erythropoiesis to replace corpuscles lost due to worms. But the cumulative loss of iron and other nutrients could be rectified by giving supplementary food alone, provided that all other requirements are met. The rate of recovery from anaemia is likely to be very slow without nutrient supplements, and studies of haemoglobin concentration after anthelmintic treatment may need to last for a year or more to show the full effect of treatment alone. The same could be said for measuring the effect of anthelmintic treatment on growth.

It would be helpful for any future meta-analysis of the effects of anthelmintic treatments if any new research studies of the impact of treatment on outcomes such as growth or haemoglobin concentration had certain key features.

1. The study should be done where worms and undernourished children are common. A prevalence of infections with intestinal nematode worms of more than 70% is suggested, and where > 20% of children are underweight or > 40% are anaemic.
2. A randomised, controlled design should be used. If individuals are randomised to treatment and control groups then a placebo should be used; if clusters are randomised, then a placebo is ideal, but not essential. To overcome the problem of not giving a treatment to subjects in a cluster trial without a placebo, both groups could be given some other treatment, such as vitamin A.
3. A sample size calculation should be done. As a rule of thumb there should be a minimum of 250 subjects in each group in a randomised trial. In a cluster trial there should be more than 25 clusters per group and a design effect of 2 should be applied.
4. Anthelmintic treatment should be given at least every 6 months. Ideally initial egg counts should be reduced by >70% by the first treatment.

This could mean giving repeated treatment initially to achieve a high efficacy, unless an effectiveness trial is being done.

5. If more than one anthelmintic is given, such as praziquantel with albendazole, or albendazole with micronutrient supplements, a 2 x 2 factorial design should be considered.
6. The key outcomes to be measured are weight and height. It may be helpful to measure triceps skinfold thickness and mid upper arm circumference to distinguish between increased adiposity and growth in tissues. If infections with hookworms or *T.trichiura* are common, then the haemoglobin concentration should be measured as well with, ideally, a measure of iron status such as ferritin or transferrin receptor (WHO/CDC, 2005).
7. If growth is to be measured, the study should last a minimum of one year, and two years if possible. Specific criteria that state when a study should be stopped may need to be set.
8. If the haemoglobin concentration is to be measured the study should last a minimum of 12 weeks, and should be continued to 52 weeks if possible if no micronutrient supplements are given after treatment.
9. Drug efficacy should be assessed 21 days after each round of treatment as a matter of good practice, to assess the development of any anthelmintic resistance.
10. The gains in any parameter related to growth should be standardised as mean gain per year. The mean and standard deviation of all outcome measures and any derived indices should be given in any report or paper for each group, with the sample sizes. If subjects are studied in clusters, then this should be taken into account during the analysis.

6.5 Implications for programmes

Deworming is an easy and inexpensive thing to do, and the drugs are very safe. Treatment can be popular with parents (Brooker et al., 2001). Most anthelmintics can be given as a single dose so no adjustment for body weight is necessary, and a single 400 mg tablet of albendazole or 500 mg of mebendazole can be given to all children older than 1 year (WHO, 2002b),

though a syrup should be given to very young children. The United Nations Children's Fund in Ethiopia have issued warnings that young children should not be forced to take tablets because of the risk of choking. Anthelmintic drugs should not be given in the first trimester of pregnancy (WHO, 1994b). Anthelmintic drugs are usually available over the counter and do not require a prescription, except in developed countries.

Over the last few years the costs of albendazole and mebendazole have been reduced to less than 5 US cents a tablet when bought in large quantities and, according to the WHO, these drugs can be given safely to all children once a year in areas where the prevalence of infection is more than 20% and twice a year where the prevalence is more than 50% (WHO, 2006). The new recommendations are shown in Table 14. To promote mass deworming the World Health Assembly in 2001 passed resolution WHA54.19 asking countries to administer anthelmintic treatments annually to at least 75% of all school-age children at risk of morbidity by 2010 (WHO, 2002a).

Insert Table 14 here

There are three justifications for giving mass treatment at least once a year in areas where the prevalence of infection with all species of intestinal nematode worms is greater than 50%.

First, because the probability of disease increases exponentially above a prevalence of 50% (see Figure 3).

Second, the cost of diagnosis is typically many times the cost of treatment. When the prevalence is greater than 50% diagnosis becomes a matter of identifying uninfected people who do not need treatment, and so the cost per case of finding them increases with the prevalence.

Third, most anthelmintic drugs, and the benzimidazoles in particular, are very safe, and there is no known harm in treating people who are not infected. Benzimidazoles have been taken daily for long periods to treat hydatid disease (El-On, 2003, Horton, 2003a) and when used to treat intestinal nematodes the overall frequency of side effects is about 1% (Horton, 2000). Although one of the potential studies identified for the meta-analysis reported evidence of an adverse effect on the growth of children given 400 mg albendazole given for 3 days, there was no untreated control group (so the study was excluded from the present analysis) and the children treated with

albendazole were compared with children treated with another anthelmintic, pyrantel embonate (Forrester et al., 1998).

The use of a 20% threshold at which to apply annual mass treatment in school-age children has cost-benefit implications. When the prevalence of infection is less than 50% the majority of children are uninfected and perhaps only a few percent of children will actually benefit from treatment. Although the cost per child treated may be small in terms of the cost of each tablet, as the prevalence drops the costs per infected child treated will increase. This is shown in Figure 26 for a drug costing 3 US cents per treatment. When the prevalence is 50% the cost per infected child treated is twice the cost per child treated, or 6 US cents per child; when the prevalence is only 20% the cost per infected child treated is five times the cost per child treated or 15 US cents per child; and if only 5% of all children actually benefit from treatment the cost per beneficiary is 20 times the cost of the treatment or 60 US cents per child.

Although these unit costs may seem small in absolute terms, the total cost to a government may be large. For example if the Ethiopian government was considering treating the 11.5 million children enrolled in primary schools in 2005 with a drug costing 3 US cents per treatment, and if the prevalence of infection according to a recent national survey is 30% (SC/US, 2007), then of the \$345,000 it will cost to buy drugs, 70% or \$241,500 will be spent on treating uninfected children.

These costs do not take into account the additional financial or opportunity costs of delivering and administering tablets.

Insert Figure 26 here

The main issue for deworming programmes is how to deliver treatments at low cost to the three main groups who would benefit most from treatment: pre-school children, school-age children, and women of reproductive age.

As there are many current programmes delivering treatments such as vaccinations and vitamin A to children less than 5 years, the additional cost of giving a tablet of albendazole or mebendazole is minimal. In recognition of this, the WHO and UNICEF now recommend deworming children as a part of all routine health programmes, such as when vitamin A is given (WHO/UNICEF, 2004), and anthelmintic treatment is also recommended as a

part of the Integrated Management of Childhood Illnesses after any acute illness has ceased.

A commonly unrecognised concern arises because of the lack of overlap between health programmes for pre-school children, which typically stop at 5 years of age, and programmes for school children, which begin when children enrol in school. As the official age of enrolment in basic education in many countries is 6 or even 7 years of age, even if all children actually enrol in school at the correct age, there is a gap of 1 – 2 years when they may fall between programmes and miss out on treatment. As late-enrolment in school is very common in sub-Saharan Africa (Partnership for Child Development, 1998b) and late enrolment is strongly associated with stunted growth and anaemia (Partnership for Child Development, 1999b, Hall et al., 2001) the gap between programmes may be as much as four or five years, and such children may be in greater need of treatment than those who are actually in school.

In countries where enrolment rates are high, school health programmes offer an effective mechanism to reach a large proportion of school-age children (Hall et al., 1996), an age group that harbours a large proportion of all worms in a community. The cost of delivering anthelmintics to schoolchildren has been shown to be a few US cents per child (Partnership for Child Development, 1999a, Partnership for Child Development, 1998a). In addition to the potential nutritional benefits of treatment, periodically giving anthelmintics to school children alone has other benefits, as it can serve to bring down transmission to other, untreated groups (Butterworth et al., 1991, Bundy et al., 1992b, Asaolu et al., 1991). Such externalities as they are called by economists, are not captured in a meta-analysis such as this, which examines only one outcome at a time.

It is also possible that, as well as affecting growth and micronutrient status, intestinal nematodes may affect children's cognitive function and educability, although the evidence for this is mixed and often comes from cross-sectional associations, which are easily confounded (Dickson et al., 2000b, Nokes et al., 1992a, Nokes et al., 1992b, Watkins and Pollitt, 1997, Jukes et al., 2002, Sakti et al., 1999). The Cochrane Review of 2007 concluded that there was insufficient evidence that treating worms improves

cognitive performance, which included educational outcomes including attendance and tests of educational achievements (Taylor-Robinson et al., 2007). The controlled trial of six-monthly deworming for two years in Viet Nam found no statistically significant difference between treatment and controls in terms of tests of mathematics and Vietnamese (Partnership for Child Development, 2001).

The last group that would benefit considerably from periodic anthelmintic treatment are women of reproductive age, although treatment should only be given before pregnancy or after the first trimester. Nevertheless accidental treatment does not seem to be dangerous: a study of some 400 Sri Lankan women who had taken mebendazole during their first trimester of pregnancy did not find a greater rate of congenital defects than in pregnant women who had not taken the drug (de Silva et al., 1999). But the sample size was too small to detect a greater risk of rare congenital defects, so the recommendation of the study was still to avoid treatment with anthelmintics (de Silva et al., 1999).

The main effect of anthelmintic treatment on pregnant women is likely to be on haemoglobin concentration as a result of treating infections with hookworm or *Schistosoma* spp. A randomised controlled trial in Sierra Leone of giving albendazole to pregnant women after their first trimester prevented a fall in haemoglobin concentration of 6.6 g/L (Torlesse and Hodges, 2001, Torlesse and Hodges, 2000). When albendazole was given with iron, both treatments prevented a fall in haemoglobin concentration of 13.7 g/L (Torlesse and Hodges, 2001, Torlesse and Hodges, 2000).

As a general rule for all programmes in which anthelmintic treatment for worms is given, drugs should not be administered to individuals who are sick for any reason. This is not because the drug may be ineffective, though it may be if there is diarrhoea. The reason for not giving treatment is because of the possibility that the subject may die of a pre-existing illness, and it could be concluded that the anthelmintic had caused the death. In any programme in which very large numbers of children are being treated on the same day, such an event becomes increasingly statistically probable, so every effort should be made to ensure that only otherwise healthy children are treated. A possible example of this was the >30 deaths reported after the administration

of vitamin A to some 3 million young children in the state of Assam in India in 2001 (West and Sommer, 2002), although there was some concern that children may have been overdosed (Kapil, 2004, Kapil, 2002). Reports of deaths of schoolchildren during mass deworming have not been documented.

The other concern during mass treatment campaigns is for adolescent girls who may be pregnant and either not know it, or be afraid to report it. Teratogenic effects of drugs are most likely to occur during the first few weeks of pregnancy, a period when a woman may not yet be aware that 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 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). In an analysis of official education statistics, also in Tanzania, pregnancy was reported to be a cause of school drop out for 6 or 7 girls per 1,000 in grades 6 and 7 respectively (Partnership for Child Development, 1998b).

These data should provide a warning to programmes that give mass treatment with anthelmintic drugs to school-age children as well for those considering adding mega-dose supplements of vitamin A to treat vitamin A deficient or anaemic adolescent girls. It cannot be assumed that adolescent girls are not pregnant.

6.6 Conclusions

Treating intestinal nematode worms can lead to significantly better weight gain and growth when treated children are compared with untreated controls.

The magnitude of the effect of treatment is specific to local epidemiological circumstances, and not all infected children will benefit to the same degree, if at all.

If no significant effect of anthelmintic treatment is detected in a study, it cannot be assumed that worms did not contribute to undernutrition; it is likely that removing worms is insufficient to lead to improved growth without extra food and nutrients.

The maximum size of any effect of treating worms cannot be estimated; studies can only indicate what difference is achievable. To show a significant

effect it is necessary to have an untreated control group and a sufficient period of follow up. This is likely to become less tenable given the measured benefits of treating worms that have been shown. Nevertheless it would be useful to have more studies of the effectiveness of anthelmintics delivered through health programmes, especially those that focus on pre-school and school-age children, and perhaps given with multiple micronutrients to make sure that no vitamin or mineral is a factor limiting catch-up growth.

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8. Tables of papers considered for review (see separate file: Worm Review Tables.doc)

9. References

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Table 1. The names of the most common intestinal helminth infections of humans, their infectious stages, the obligatory intermediate host, and the stage that is infectious to humans.

Latin name	English name	Class or Phylum	Infectious stage in faeces	Intermediate host	Stage infectious to humans
<i>Fasciolopsis buski</i>	Intestinal fluke	Trematoda	Egg	Water snail	Metacercaria on vegetation
<i>Echinostoma</i> spp	Intestinal fluke	Trematoda	Egg	Water snail	Metacercaria in snails
<i>Taenia^a saginata</i>	Beef tapeworm	Cestoidea	Egg in proglottid	Cow and bovids	Cysticercus in beef
<i>Taenia^a solium</i>	Pork tapeworm	Cestoidea	Egg in proglottid	Pig and swine	Cysticercus in pork
<i>Hymenolepis nana</i>	Dwarf tapeworm	Cestoidea	Egg in proglottid	Beetle, flea	Cysticercoid in insect
<i>Hymenolepis diminuta</i>	Rat tapeworm	Cestoidea	Egg in proglottid	Insect	Cysticercoid in insect
<i>Diphyllobothrium latum</i>	Fish tapeworm	Cestoidea	Egg	Fish	Plerocercoid in raw fish
<i>Enterobius vermicularis</i>	Pinworm	Nematoda	Egg	No	Larva in egg shell
<i>Strongyloides stercoralis</i>	Threadworm	Nematoda	Egg or larva	No	Free-living larva
<i>Ascaris lumbricoides</i>	Large roundworm	Nematoda	Egg	No	Larva in egg shell
<i>Trichuris trichiura</i>	Whipworm	Nematoda	Egg	No	Larva in egg shell
<i>Ancylostoma duodenale</i>	Hookworm	Nematoda	Egg	No	Free-living larva
<i>Necator americanus</i>	Hookworm	Nematoda	Egg	No	Free-living larva

^a Also known as genus *Taeniarhynchus*

Table 2. Estimated fecundity of fertilised females of the major species of intestinal nematode worms. Data from (Sinniah, 1982, Anderson and May, 1991, Bundy and Cooper, 1989). The numbers are based on very few data and do not take into account density dependent fecundity or geographical variation in fecundity. At best they can be considered as indicative of the relative orders of magnitude of egg production.

Species	Eggs/female worm
<i>Ascaris lumbricoides</i>	< 200,000
<i>Trichuris trichiura</i>	3,000 – 20,000
<i>Ancylostoma duodenale</i>	10,000 – 20,000
<i>Necator americanus</i>	3,000 – 6,000

Table 3. Estimates of the population and number of people infected in millions, and the prevalence of infection with the main types of intestinal nematodes by region and age group. Data extracted from (de Silva et al., 2003).

<i>Ascaris lumbricoides</i>	Popul- ation	Age range (years)				Total	% infected
		0-4	5-9	10-14	≥ 15		
Latin American & Caribbean	530	8	10	10	56	84	15.8
Sub-saharan Africa	683	28	28	25	92	173	25.3
Middle east & north Africa	313	3	3	3	14	23	7.3
South Asia	363	13	15	13	56	97	26.7
India	1027	15	18	17	89	139	13.5
East Asia & the Pacific	564	20	25	25	134	204	36.2
China	1295	35	44	51	371	501	38.7
Total	4775	122	143	144	812	1221	25.6

<i>Trichuris trichiura</i>	Popul- ation	Age range (years)				Total	% infected
		0-4	5-9	10-14	≥ 15		
Latin American & Caribbean	530	10	12	12	66	100	18.9
Sub-saharan Africa	683	26	27	23	86	162	23.7
Middle east & north Africa	313	1	1	1	4	7	2.2
South Asia	363	10	11	10	43	74	20.4
India	1027	8	9	9	47	73	7.1
East Asia & the Pacific	564	16	19	19	105	159	28.2
China	1295	15	19	22	163	219	16.9
Total	4775	86	98	96	812	1092	22.9

Hookworm	Popul- ation	Age range (years)				Total	% infected
		0-4	5-9	10-14	≥ 15		
Latin American & Caribbean	530	1	3	5	41	50	9.4
Sub-saharan Africa	683	9	18	29	142	198	29.0
Middle east & north Africa	313	0	1	1	8	10	3.2
South Asia	363	2	5	8	44	59	16.3
India	1027	2	5	8	56	71	6.9
East Asia & the Pacific	564	4	9	16	120	149	26.4
China	1295	3	9	18	173	203	15.7
Total	4775	21	50	85	584	740	15.5

Table 4. The estimated number and percentage of children aged 5 – 9 years infected with the three main species of soil-transmitted helminths and the population at risk in 2002 derived from (de Silva et al., 2003) and (Hall and de Silva, 2007) in the main geographic areas covered by the WHO. Data for some countries are missing. The estimate for the number and percentage infected with any of these three species has assumed that where they are endemic, they occur in the same populations and that the chances of being concurrently infected with two or more species are independent.

World Bank regions	Population	<i>Ascaris lumbricoides</i>		<i>Trichuris trichiura</i>		Hookworms		Any species	
	No x 10 ⁶	No x 10 ⁶	%	No x 10 ⁶	%	No x 10 ⁶	%	No x 10 ⁶	%
Asia & W. Pacific	124.2	56.3	45.3	27.6	22.3	12.3	9.9	76.6	61.7
South-east Asia B	28.4	9.6	33.6	9.6	33.9	5.3	18.6	18.3	64.3
South-east Asia D	147.3	33.0	22.4	21.2	14.4	9.1	6.2	55.5	37.7
Americas B	45.0	7.0	15.5	8.8	19.5	2.2	4.8	15.8	35.2
Americas D	9.1	3.4	37.7	3.2	35.0	0.9	9.5	5.8	63.3
Middle east B	15.3	1.0	6.7	0.0	0.3	0.0	0.2	1.1	7.1
Middle east D	47.2	5.0	10.6	1.4	3.0	1.2	2.6	7.3	15.5
Africa D	44.6	13.3	29.7	10.0	22.3	7.6	17.0	24.4	54.7
Africa E	51.9	14.8	28.6	16.9	32.5	10.1	19.4	31.7	61.1
Total	513.0	143.4	27.9	98.7	19.2	48.6	9.5	242.8	47.3

Table 5. The threshold concentrations of worm eggs in faeces used to classify infections as light, moderate and heavy proposed by a WHO Expert Committee in 2002 (WHO, 2002a). No references or data are given in support of these numbers.

Intensity	<i>Ascaris lumbricoides</i>	<i>Trichuris trichiura</i>	Hookworms
Low	1- 4,999	1 – 999	1 – 1,999
Moderate	5,000 – 49,999	1,000 – 9,999	2,000 – 3,999
High	≥ 50,000	≥ 10,000	≥ 4,000

Table 6. Estimates of the life span of the major species of intestinal nematode worms of humans (data from (Anderson and May, 1991)).

Species	Life span (years)
<i>Ascaris lumbricoides</i>	1 – 2 y
<i>Trichuris trichiura</i>	1 – 2 y
<i>Ancylostoma duodenale</i>	2 – 3 y
<i>Necator americanus</i>	2 – 3 y
<i>Enterobius vermicularis</i>	< 1 y
<i>Strongyloides stercoralis</i>	> 50 y ^a

^a Resulting from auto-infection

Table 7. The typical range in cure rates of drugs to treat intestinal nematode infections. The doses are those recommended by the World Health Organization (WHO, 1995). The data for the drugs that paralyse worms have been derived from (Albonico et al., 2003, Gustafsson et al., 1987, Huq et al., 1982). The data for the metabolic inhibitors is summarised from (Bennett, 2000), and represents the approximate inter-quartile range in an analysis of multiple studies of drug efficacy. The data have been combined for the metabolic inhibitors albendazole and mebendazole, except for hookworm, for which there is a difference between species in efficacy.

Species	Drugs that paralyse		Metabolic inhibitors	
	Cure rate	ERR ^a	Cure rate	ERR
<i>Ascaris lumbricoides</i>	80 - 100 %	95 – 100%	95 – 99 %	99 – 100%
<i>Ancylostoma duodenale</i>	80 – 100%	50 – 70%	70 – 90% ^b	75 – 95% ^b
<i>Necator americanus</i>	60 – 90%		20 – 80% ^c	55 – 95% ^c
<i>Trichuris trichiura</i>	Poor ^d	20 – 60%	10 – 70%	50 – 90%

^aERR = egg reduction rate; ^b Albendazole 400 mg; ^c Mebendazole 500 mg; ^dUnless pyrantel given with oxantel

Table 8. Data from a study in Zanzibar of the efficacy of treating intestinal nematode infections with either albendazole or mebendazole (Albonico et al., 1994). Even though the drugs have a very similar mode of action there were statistically significant differences in the cure rates and egg reduction rates, particularly for hookworms.

Species	Drug	n	Cure rate	Egg reduction rate
<i>Ascaris lumbricoides</i>	Albendazole	1,174	98.9	99.6
	Mebendazole	1,120	97.8	99.3
Hookworms	Albendazole	1,174	56.8***	97.7***
	Mebendazole	1,120	22.4	82.4
<i>Trichuris trichiura</i>	Albendazole	1,174	10.5**	73.3***
	Mebendazole	1,120	14.2	81.6

** = $P < 0.01$; *** = $P < 0.001$

Table 9. The terms used to search Medline for papers. MeSH denotes a specific Medical Subject Heading used as a search term.

Worms	Treatments	Outcomes
"intestinal worms" "intestinal parasites" geohelminth* helminth* Ascaris roundworm Trichuris whipworm Necator ancylostoma hookworm	deworm* de-worm* anthelmintic* antihelmintic* vermifuge benzimidazole albendazole mebendazole pyrantel levamisole piperazine	weight height length growth skinfold "arm circumference" "nutritional status" malnutrition anthropometr*
"Ascaris lumbricoides" [MeSH] Trichuris [MeSH] "Necator americanus" [MeSH] "Ancylostoma duodenale" [MeSH]	"Ascariasis/drug therapy" [MeSH] "Ascariasis/prevention and control" [MeSH] "Ascariasis/therapy" [MeSH] "Hookworm infections/drug therapy" [MeSH] "Hookworm infections/prevention and control" [MeSH] "Hookworm infections/therapy" [MeSH] "Trichuriasis/drug therapy" [MeSH] "Trichuriasis/prevention and control" [MeSH] "Trichuriasis/therapy"[MeSH]	haemoglobin hemoglobin "iron status" anaemia anemia retinol

Table 10. A summary of main characteristics of the studies included in the meta-analysis.

Authors	<i>Ascaris Trichuris</i> Hookworm			Any ^a	Age range	N	Drug ^b	Dose	Frequency	Treatment	Control
Adams <i>et al.</i> (1994).	29%	84%	93%	NR	5-10 y	56	ABZ	400 mg/d x 3 d	Once	None	Placebo
Alderman <i>et al.</i> (2006)	~ 18%	~ 7%	~44%	~ 56%	1-7 y	27,995	ABZ	400 mg	2 - 5 times every 6 mo	None	Untreated
Dossa <i>et al.</i> (2001).	38%	47%	13%	NR	3-5 y	177	ABZ	200 mg/d x 3 d	Twice, 1 month apart	Iron	Placebo
Gupta <i>et al.</i> (1982).	51-72%	9%	0%	NR	24-61 mo	159	PPZ	75 mg/kg/d x 2d	Once	None	Placebo
Koroma <i>et al.</i> (1996). Rural	46%	25%	1%	NR	6-10 y	98	ABZ	400 mg	Once	None	Placebo
Koroma <i>et al.</i> (1996). Urban	32%	10%	65%	NR	6-10 y	99	ABZ	400 mg	Once	None	Placebo
Northrop-Clewes <i>et al.</i> (2001).	78%	65%	4%	NR	2-5 y	117	PP	10 mg/kg	Single dose then	None	Placebo
							MBZ	500 mg	bi monthly for 1 year		
PCD (2002, unpublished).	71%	84%	7%	93%	7-8 y	2,659	ABZ	400 mg	Every 6 mo, 5 times	None	Untreated
Sarker <i>et al.</i> (2002).	78%	NR	NR	NR	2-12 y	85	PP	11 mg/kg	Once	None	Placebo
Simeon <i>et al.</i> (1995).	42-50%	100%	NR	NR	6-12 y	407	ABZ	400 mg/d x 2 d	Once	None	Placebo
Stephenson <i>et al.</i> (1989c).	49%	97%	87%	NR	6-16 y	150	ABZ	400 mg	Once	None	Placebo
Stephenson <i>et al.</i> (1993a).	26-35%	81-92%	85-88%	NR	6-15 y	284	ABZ	600 mg	Once or twice 3.6 m later	None	Placebo
Stephenson <i>et al.</i> (1993b).	41%	98%	96%	NR	7-13 y	53	ABZ	600 mg	Once	Food	Placebo
Stoltzfus <i>et al.</i> (1997).	66-76%	95-97%	91-96%	NR	Not stated	3063	MBZ	500 mg	2x or 3 x per year	None	Unclear
Stoltzfus <i>et al.</i> (1998).	67-76%	95-97%	91-96%	NR	Not stated	2924	MBZ	500 mg	2x or 3 x per year	Iron	Untreated
Stoltzfus <i>et al.</i> (2004).	42-44%	71-72%	54%	NR	6-71 mo	459	MBZ	500 mg	Once every 3 mo for 1 y	Iron	Placebo
Tanumihardjo <i>et al.</i> (1996)	100%	17-27%	NR	NR	0.6-6.6 y	309	ABZ	400 mg	Once	Retinol	Placebo
Tanumihardjo <i>et al.</i> (2004).	100%	28%	NR	NR	Not stated	51	ABZ	400 mg	Once	Retinol	Untreated
Thein-Hlaing <i>et al.</i> (1991).	81- 83%	5-7%	1-2%	NR	2-12 y	1206	LEV	Not stated	Once	None	Untreated
Watkins <i>et al.</i> (1996).	91-92%	78-85%	NR	NR	< 12 y	228	ABZ	400 mg	Once	None	Placebo

^a NR = Not reported; ^b ABZ = Albendazole; LEV = Levamisole; MBZ = Mebendazole; PP = Pyrantel pamoate; PPZ = Piperazine

Table 11. The countries from which data were published in papers on the effect of anthelmintic treatment on the growth and nutritional status of children. Also shown is the number of times each country is represented in papers found during the literature search and the papers eventually used in the meta-analysis. One paper reported data from China, the Philippines and Kenya (Olds et al., 1999) so the total number of papers is 58 rather than 60. All other papers only presented data from one country.

Country	Papers found	Papers used
Benin	1	1
Botswana	1	0
Ethiopia	2	0
Kenya	11	4
Sierra Leone	1	1
South Africa	4	0
Tanzania	6	3
Uganda	1	1
Zaire	1	0
China	1	0
Indonesia	7	2
Malaysia	3	0
Myanmar	1	1
Philippines	1	0
Viet Nam	1	1
Bangladesh	5	2
India	3	0
Sri Lanka	1	0
Brazil	2	0
Guatemala	2	2
Haiti	2	0
Jamaica	2	1
Mexico	1	0
Total	58	19

Table 12. Summary of changes in primary and secondary outcome measures for studies in which any drug to treat intestinal nematode worms was given. The drugs were: albendazole and mebendazole, levamisole, piperazine or pyrantel pamoate

Primary outcome measure	No. of studies	No. of participants	Estimate (95% C.I.)	<i>P</i>
Weight (kg)	11	33,860	0.21 (0.17, 0.26)	<0.001
Height (cm)	9	5,801	0.11 (0.03, 0.19)	0.01
MUAC ^a (cm)	7	3,325	0.30 (0.23, 0.37)	<0.001
Triceps skinfold (mm)	5	3,021	0.11 (0.03, 0.18)	0.04
Haemoglobin (g/dL)	5	2,178	-0.93 (-2.97, 1.10)	0.37
% DR/R ^b ratio	2	204	0.17 (-0.60, 0.93)	0.67

Secondary outcome measures	No. of studies	No. of participants	Estimate (95% C.I.)	<i>P</i>
Weight-for-age z-score	5	557	0.06 (0.03, 0.08)	<0.001
Height-for-age z-score	6	961	0.09 (0.06, 0.11)	<0.001
Weight-for-height z-score	4	378	0.38 (0.30, 0.46)	<0.001
Weight-for-age % median	4	401	2.52 (1.95, 3.08)	<0.001
Height-for-age % median	4	401	0.27 (0.12, 0.42)	<0.001
Weight-for-height % median	3	323	2.64 (1.97, 3.30)	<0.001

^a MUAC = mid upper-arm circumference

^b DR/R = dehydroretinol/retinol

Table 13. Summary of changes in primary and secondary outcome measures for studies in which albendazole or mebendazole were given to treat intestinal nematode worms.

Outcome measure	No. of studies	No. of participants	Estimate (95% C.I.)	<i>P</i>
Weight (kg)	8	33,275	0.18 (0.13, 0.23)	<0.001
Height (cm)	6	5,227	0.08 (-0.01, 0.17)	0.07
MUAC ^a (cm)	6	3,228	0.30 (0.23, 0.37)	<0.001
Triceps skinfold (mm)	5	3,021	0.11 (0.03, 0.18)	0.004
Haemoglobin (g/dL)	5	2,178	-0.93 (-2.97, 1.10)	0.37
% DR/R ^b ratio	2	204	0.17 (-0.60, 0.93)	0.67

Secondary outcome measure	No. of studies	No. of participants	Estimate (95% C.I.)	<i>P</i>
Weight-for-age z-score	4	468	0.06 (0.03, 0.08)	<0.001
Height-for-age z-score	5	855	0.09 (0.06, 0.11)	<0.001
Weight-for-height z-score	4	378	0.38 (0.30, 0.45)	<0.001
Weight-for-age % median	2	242	3.16 (2.51, 3.81)	<0.001
Height-for-age % median	2	242	0.31 (0.14, 0.47)	<0.001
Weight-for-height % median	2	242	2.73 (2.03, 3.44)	<0.001

^a MUAC = mid upper-arm circumference

^b DR/R = dehydroretinol/retinol

Table 14. The prevalence of any species of intestinal nematode that warrants mass treatment criteria for applying treatments and the target groups.

Risk category	Prevalence	Target groups and treatments	
High	≥ 50%	Treat all school-age children twice a year	Treat all: <ul style="list-style-type: none"> • pre-school children • women of child-bearing age except in first trimester • adults at risk
Low	≥ 20% to < 50%	Treat all school-age children once a year	Treat all: <ul style="list-style-type: none"> • pre-school children • women of child-bearing age except in first trimester • adults at risk

Figure 1. The proglottid of *Taenia saginata* (at the end of the stick) crawling away from a human stool in a trail of mucus. The sample was collected from a Pokot man in western Kenya, an ethnic group that traditionally enjoys eating undercooked beef (Hall et al., 1981).



Figure 2. The prevalence of infection with *A.lumbricoides* in 11 age classes of males living in an urban slum in Dhaka, Bangladesh (data from (Hall et al., 1999)).

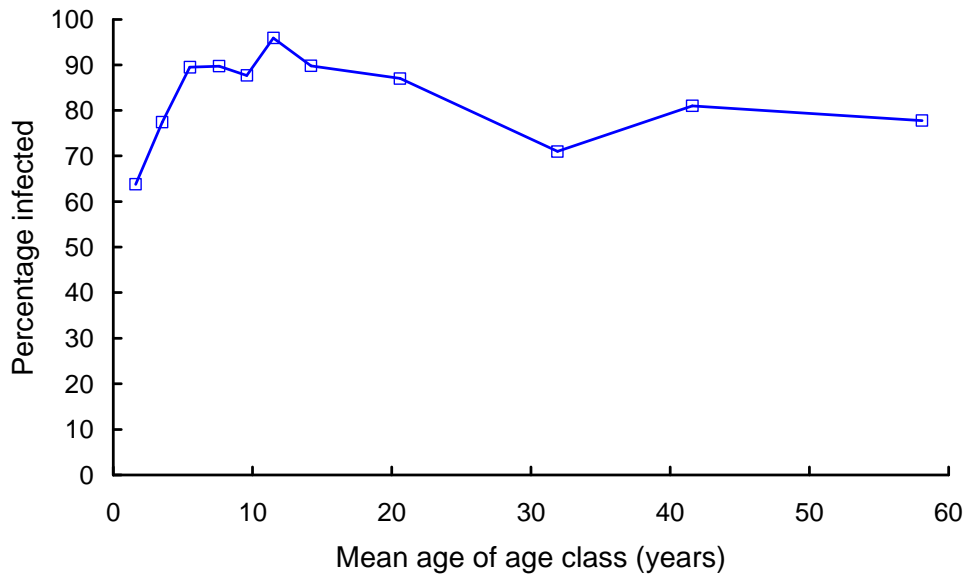


Figure 3 The typical relationship between the prevalence and the mean worm burden for intestinal nematode worms (see (Guyatt et al., 1990)). The shape of the curve is derived from data collected during a study of *A.lumbricoides* in Bangladesh (Hall et al., 1999).

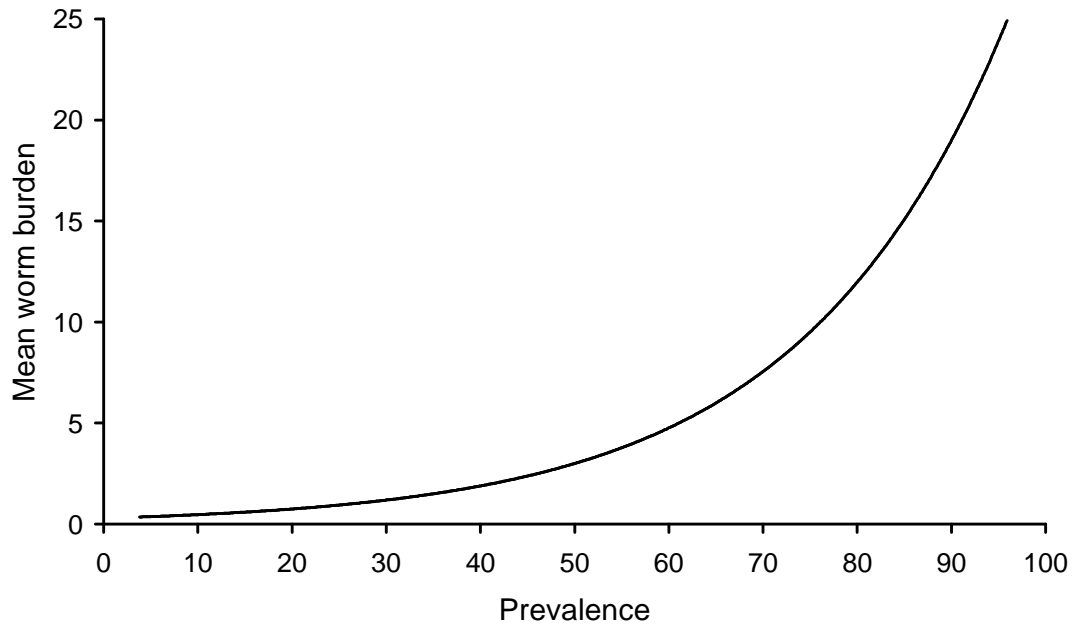


Figure 4. A diagrammatic representation of the proportions of a population of 100% who are infected with one, two or three types of worms when the prevalence of infection with *Ascaris lumbricoides* is 60%, *Trichuris trichiura* is 50% and hookworm is 40%. It is assumed that the probability of each infection is independent of each other and that probability of having two or more infections is multiplicative.

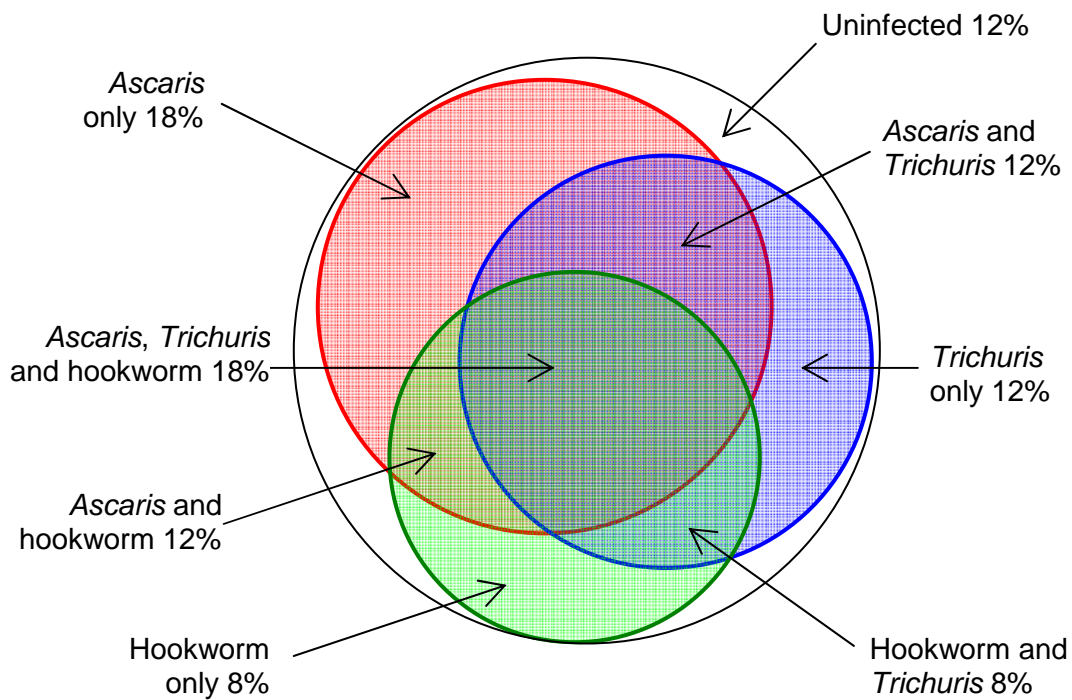


Figure 5. The average number of worms recovered from males in 11 age classes living in an urban slum in Bangladesh (Hall et al., 1999).

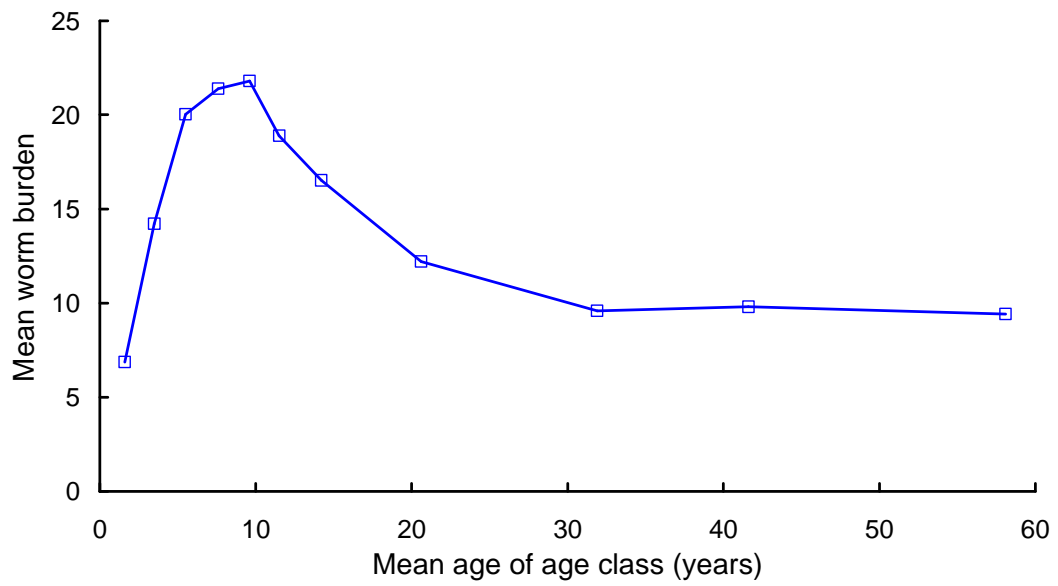


Figure 6. The distribution of *A.lumbricoides* in 1,765 people living in an urban slum in Dhaka, Bangladesh (Hall et al., 1999). The black line shows the negative binomial distribution.

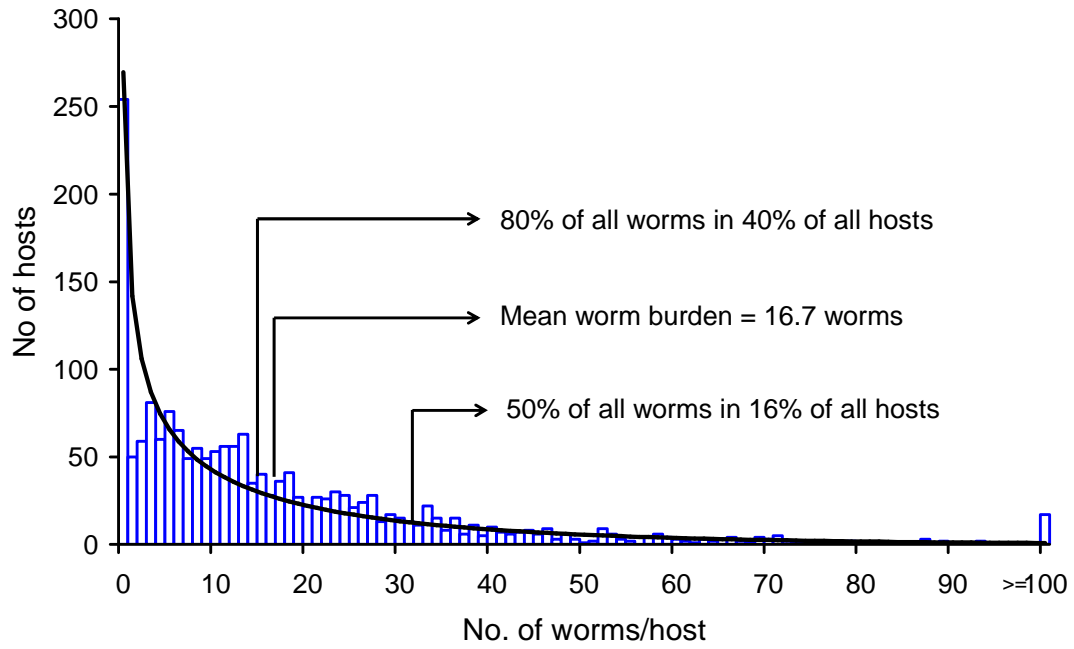


Figure 7. The cumulative percentage of worms recovered from 1,511 people infected with *Ascaris lumbricoides* in an urban slum in Bangladesh ranked according to worm burdens from zero to the maximum of 187 worms, plotted against the cumulative number of subjects from whom they were recovered (data from (Hall et al., 1999)).

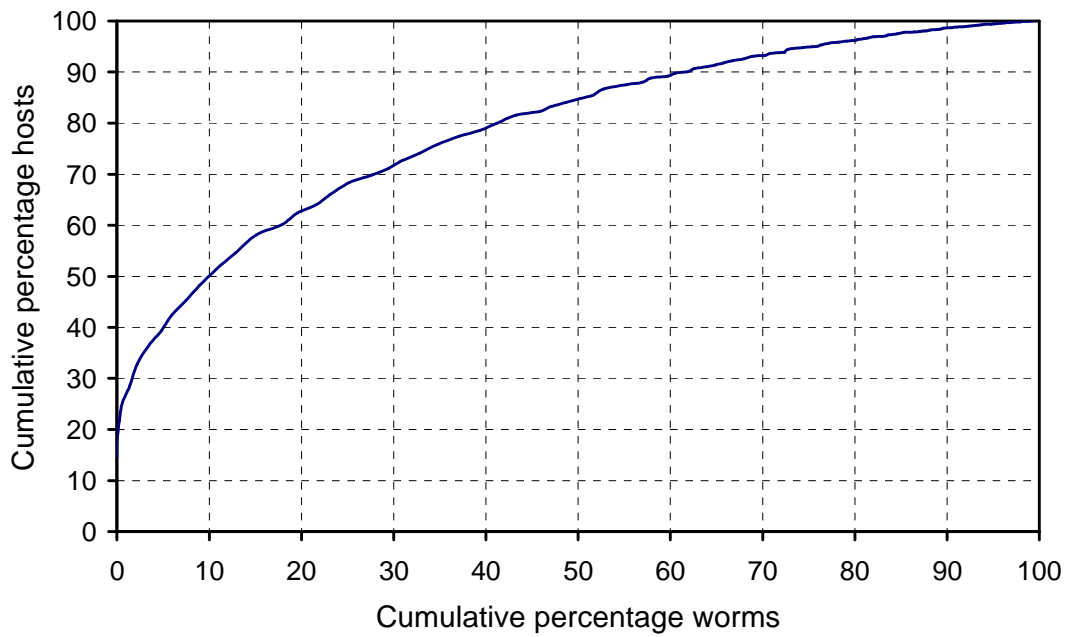


Figure 8 The prevalence of infection with *A.lumbricoides* at three rounds of treatment six months apart (Hall et al., 1992).

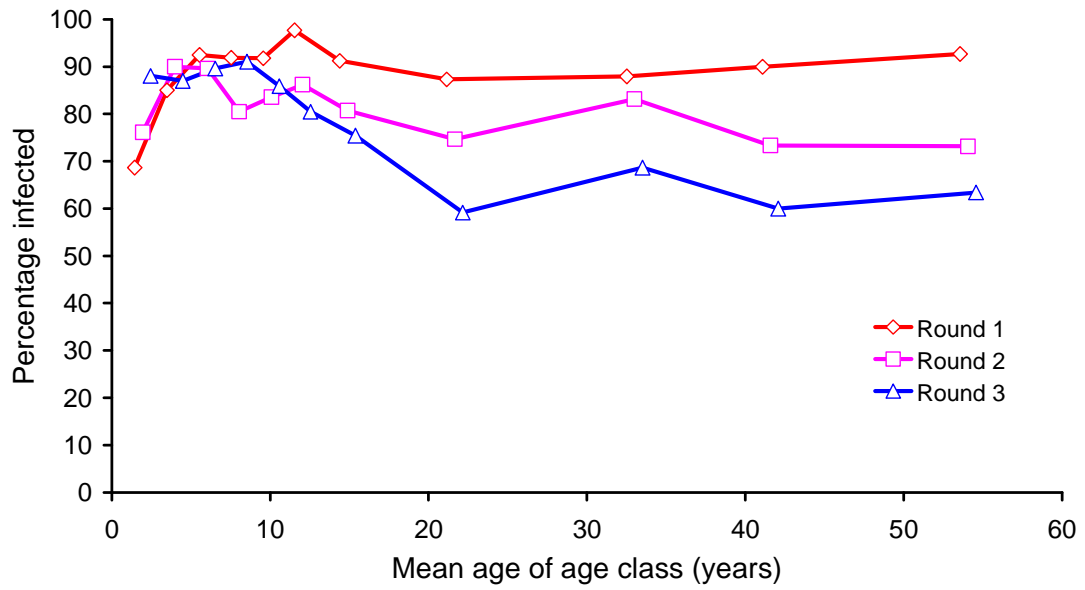


Figure 9. The mean worm burden with *A.lumbricoides* at three rounds of treatment six months apart (Hall et al., 1992).

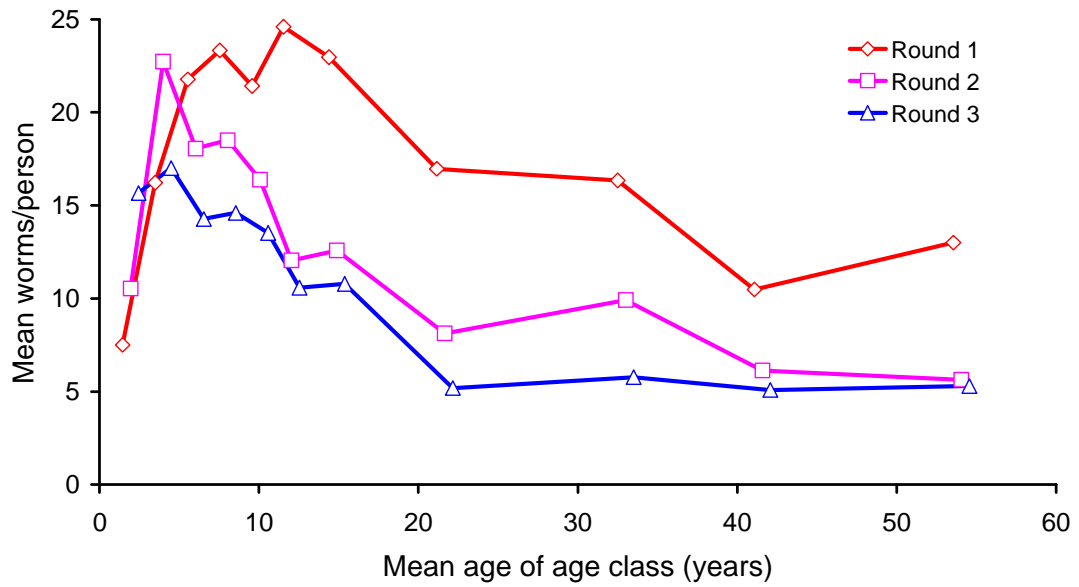


Figure 10. The prevalence of infection with *A.lumbricoides* among 445 school-age children in Bangladesh and the mean worm burden at baseline (0 months) and at two treatments six months apart (data from study of (Hall et al., 1999). The dotted lines represent extrapolated trend lines if treatments had been given twice more at six month intervals.

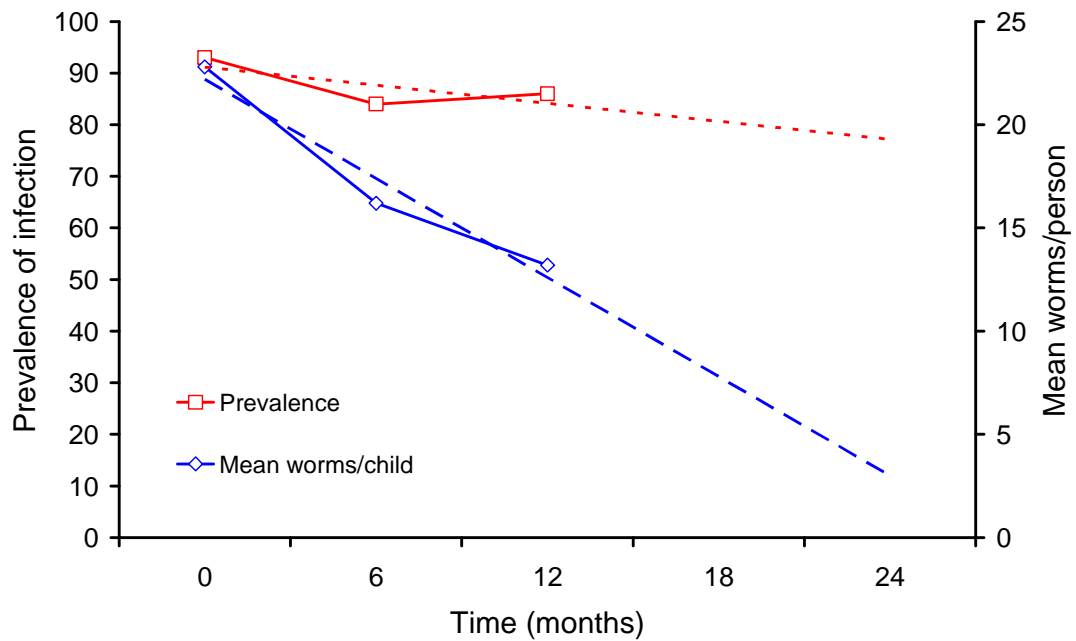


Figure 11 The average and 95% confidence intervals of body weight of two hypothetical groups of 300 children, on treated regularly with an anthelmintic and an untreated control group followed up for 3 years.

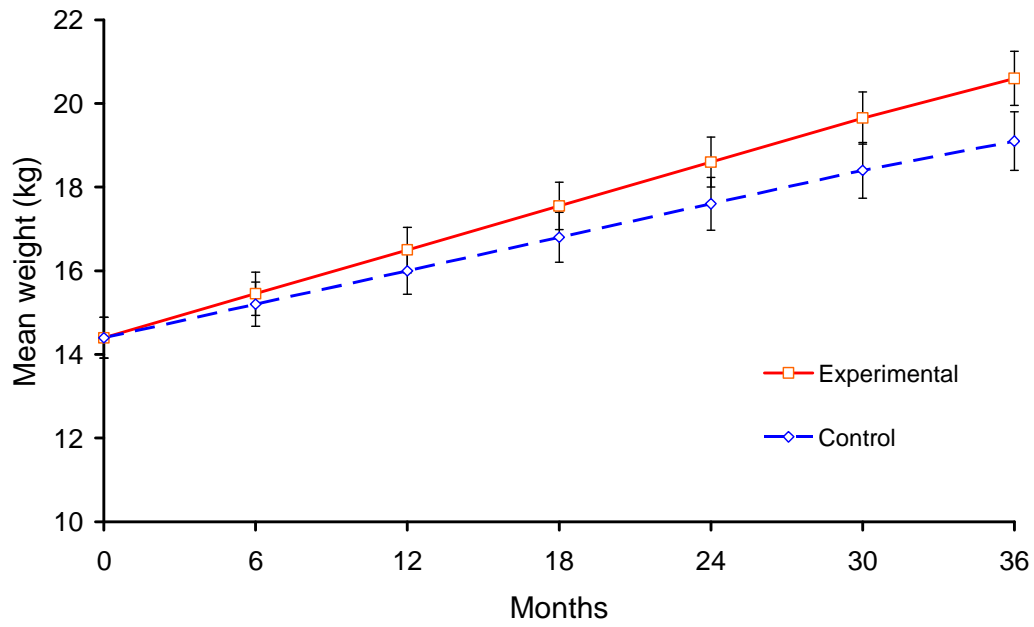


Figure 12. A conceptual model of the effect of worms on an outcome measure, and the need for remedial therapy after anthelmintic treatment to bring about a recovery.

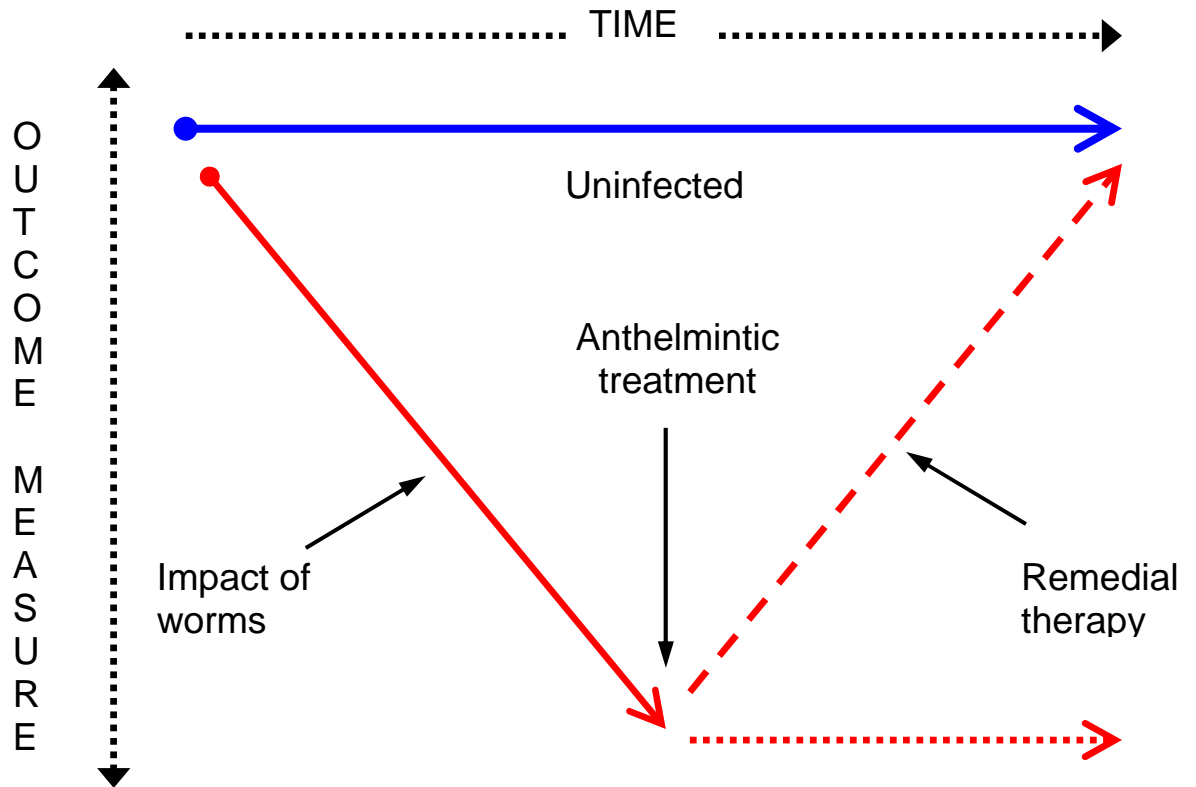


Figure 13. The effects of treating intestinal worms on body weight (kg). To interpret the figure, see Section 5.3.

Review: Effect of treating intestinal worms on children's growth and nutritional status
 Comparison: 01 Anthelmintic v. control
 Outcome: 01 Mean change in weight (kg)

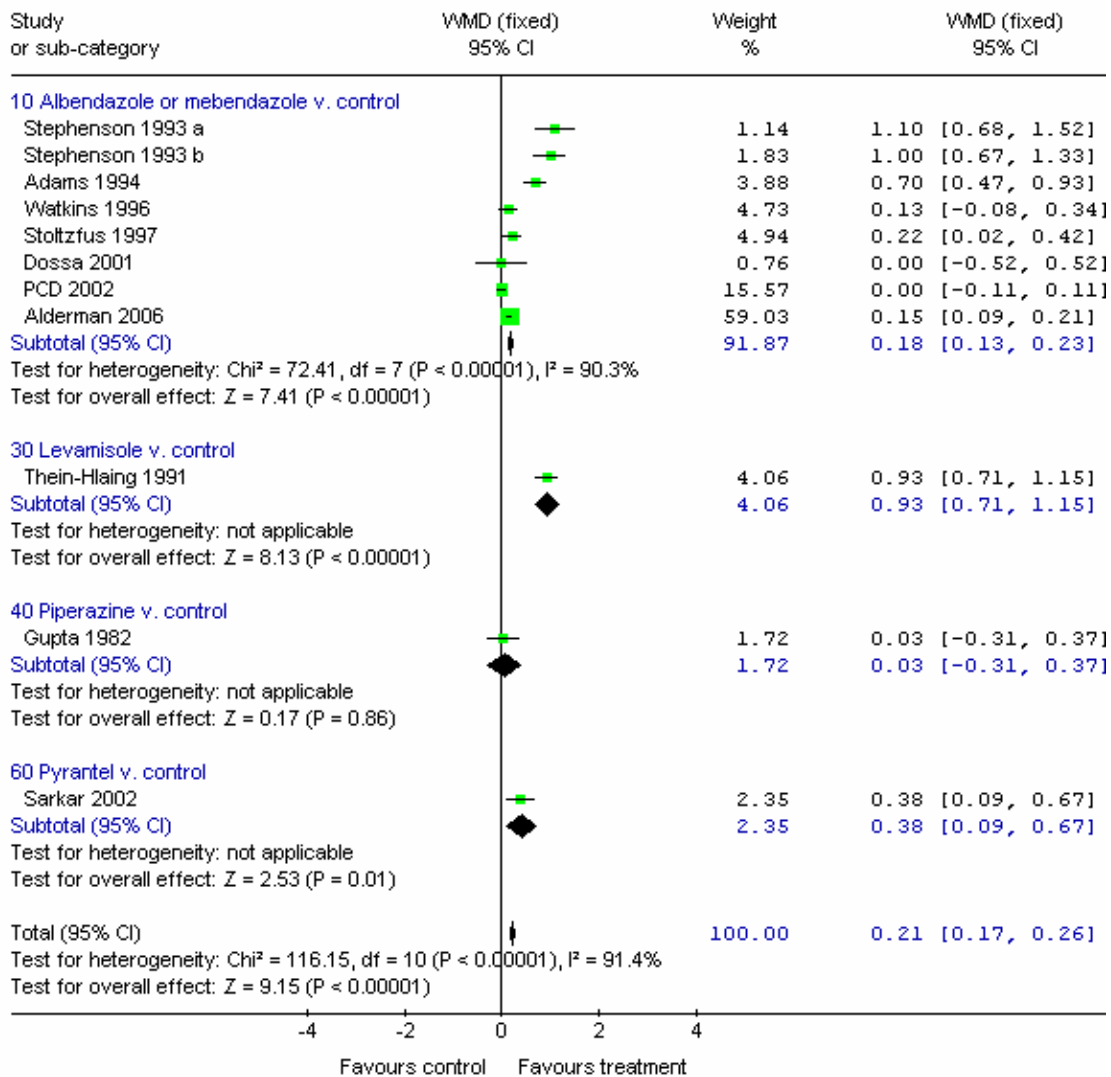


Figure 14 The effects of treating intestinal worms on height (cm). To interpret the figure, see Section 5.3.

Review: Effect of treating intestinal worms on children's growth and nutritional status
 Comparison: 01 Anthelmintic v. control
 Outcome: 02 Mean change in height (cm)

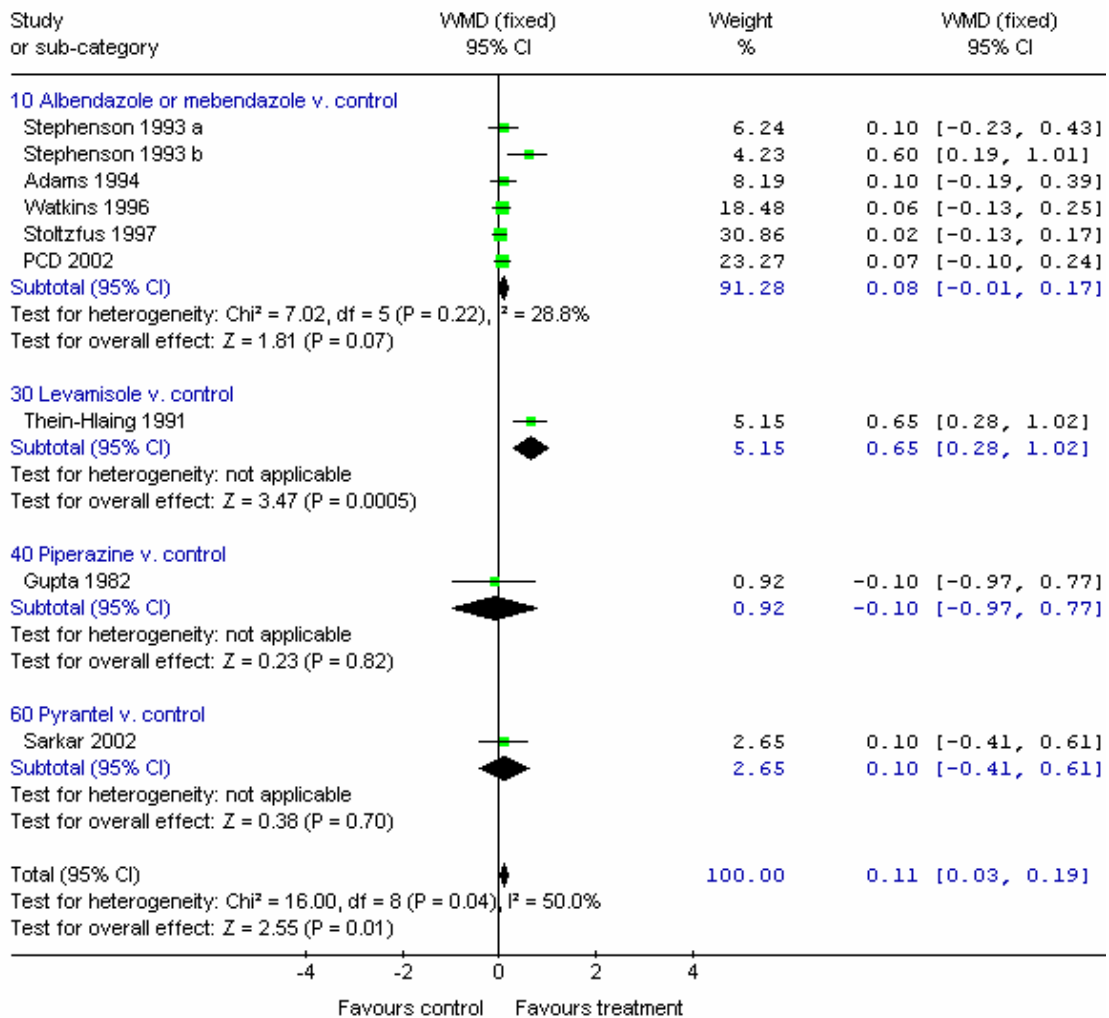


Figure 15. The effects of treating intestinal worms on mid upper-arm circumference (mm). To interpret the figure, see Section 5.3.

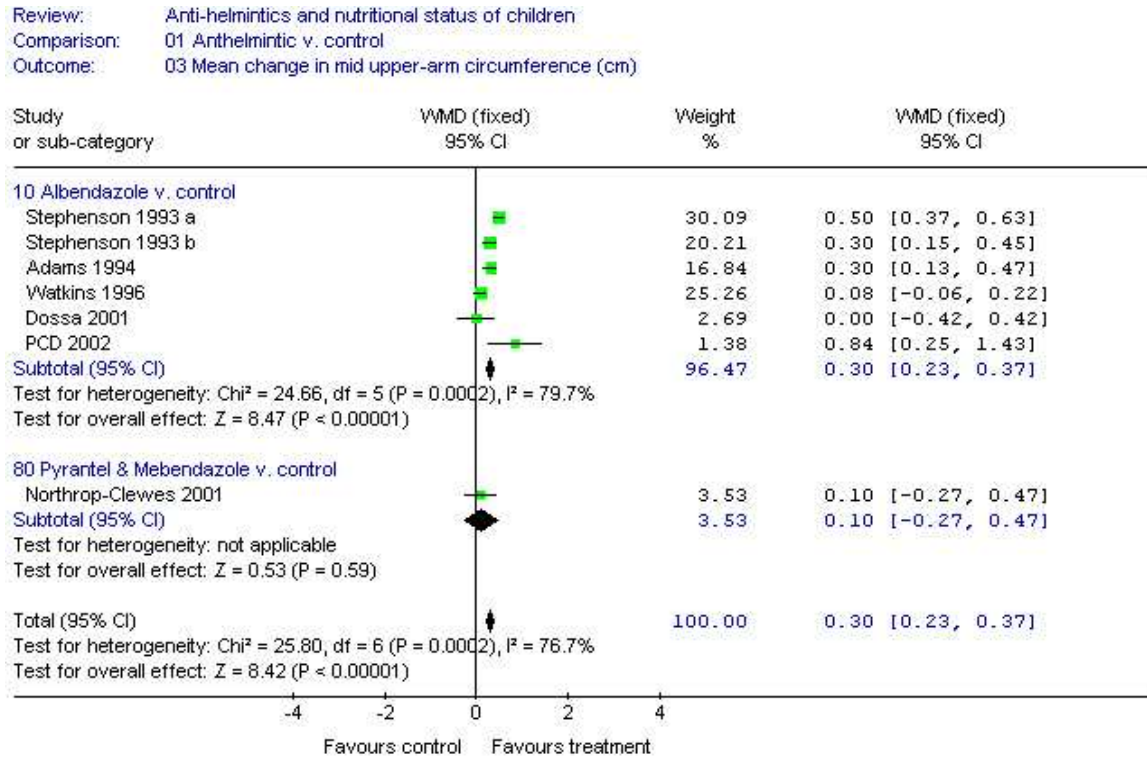


Figure 16. The effects of treating intestinal worms on triceps skinfold thickness (mm). To interpret the figure, see Section 5.3.

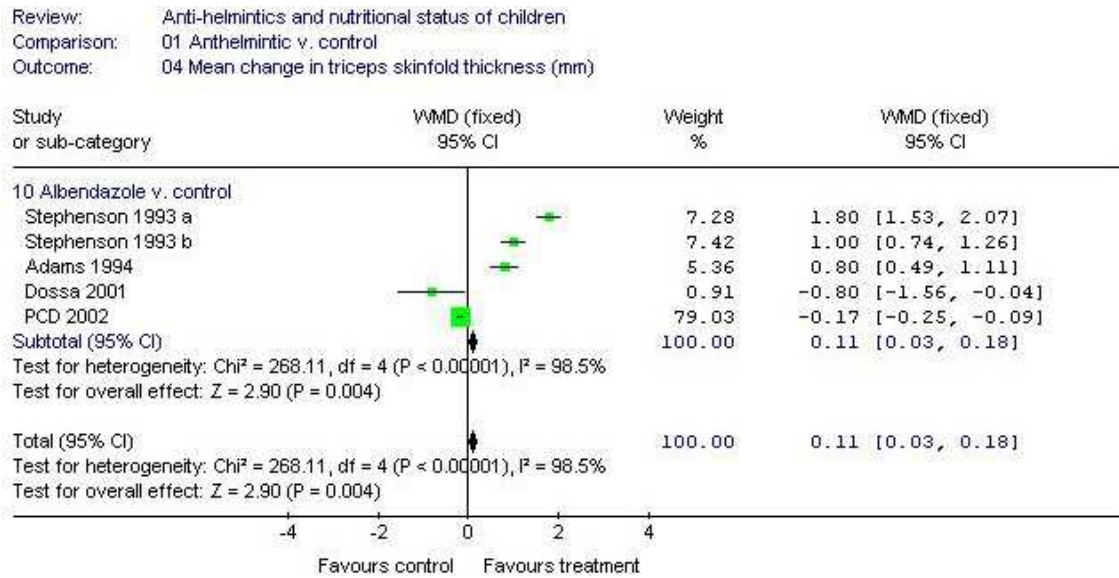


Figure 17. The effects of treating intestinal worms on z-score of weight-for-age). To interpret the figure, see Section 5.3.

Review: Effect of treating intestinal worms on children's growth and nutritional status
 Comparison: 01 Anthelmintic v. control
 Outcome: 05 Mean change in z-score of weight-for-age

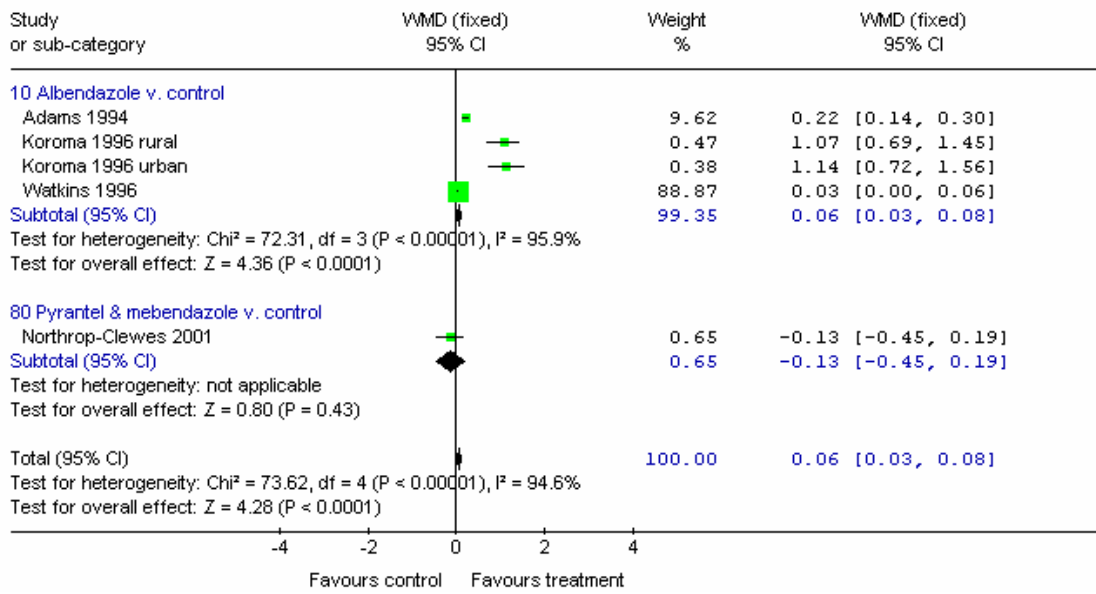


Figure 18. The effects of treating intestinal worms on z-score of height-for-age. To interpret the figure, see Section 5.3.

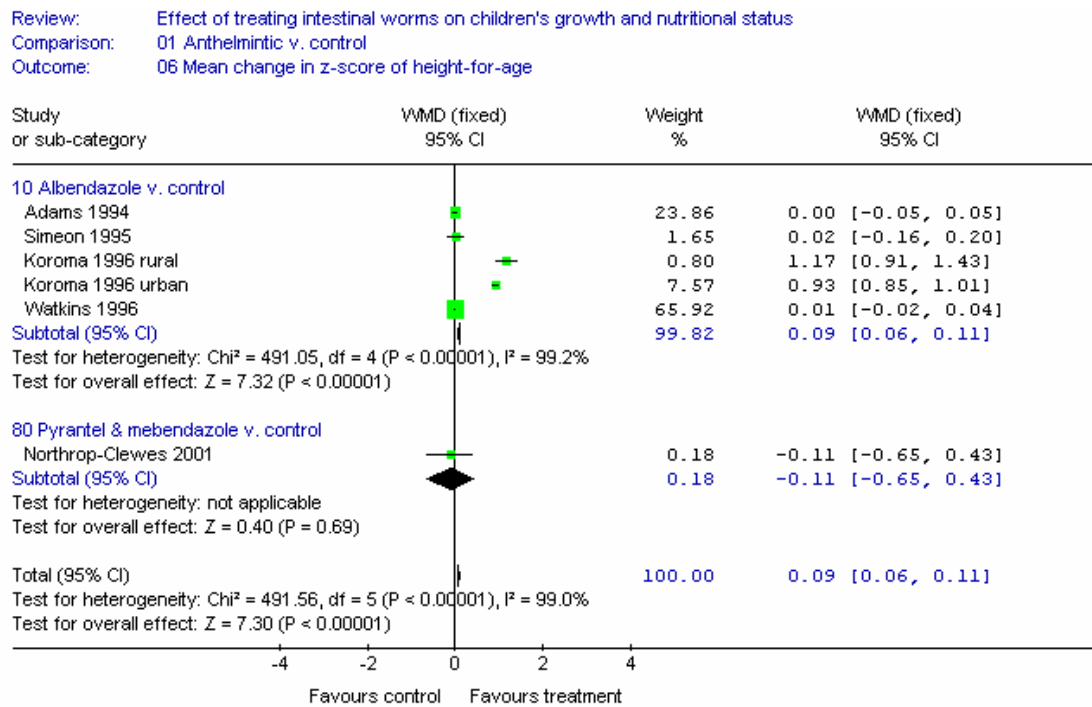


Figure 19. The effects of treating intestinal worms on the difference in z-score of weight-for-height. To interpret the figure, see Section 5.3.

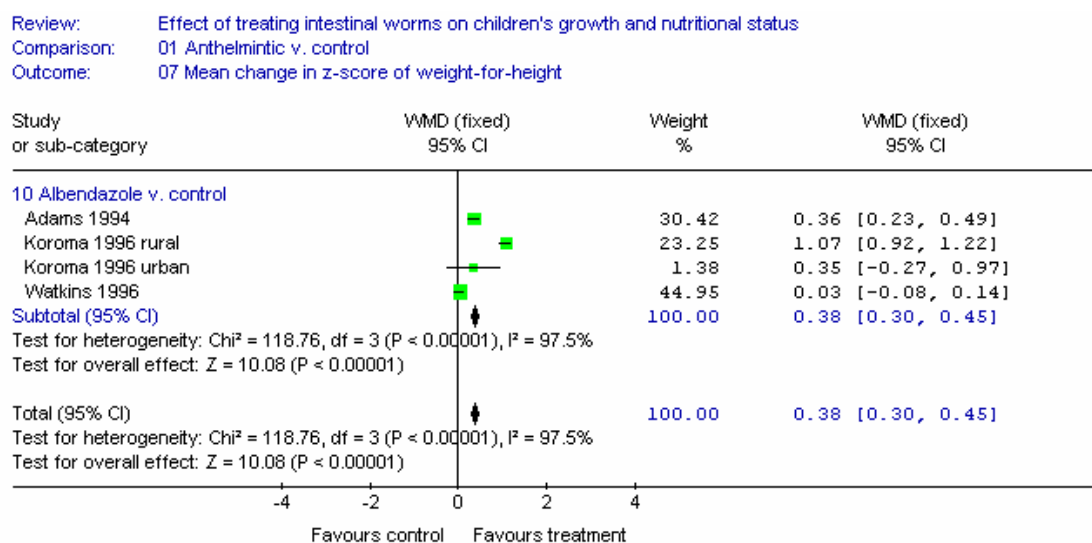


Figure 20. The effects of treating intestinal worms on percentage of the median weight-for-age. To interpret the figure, see Section 5.3.

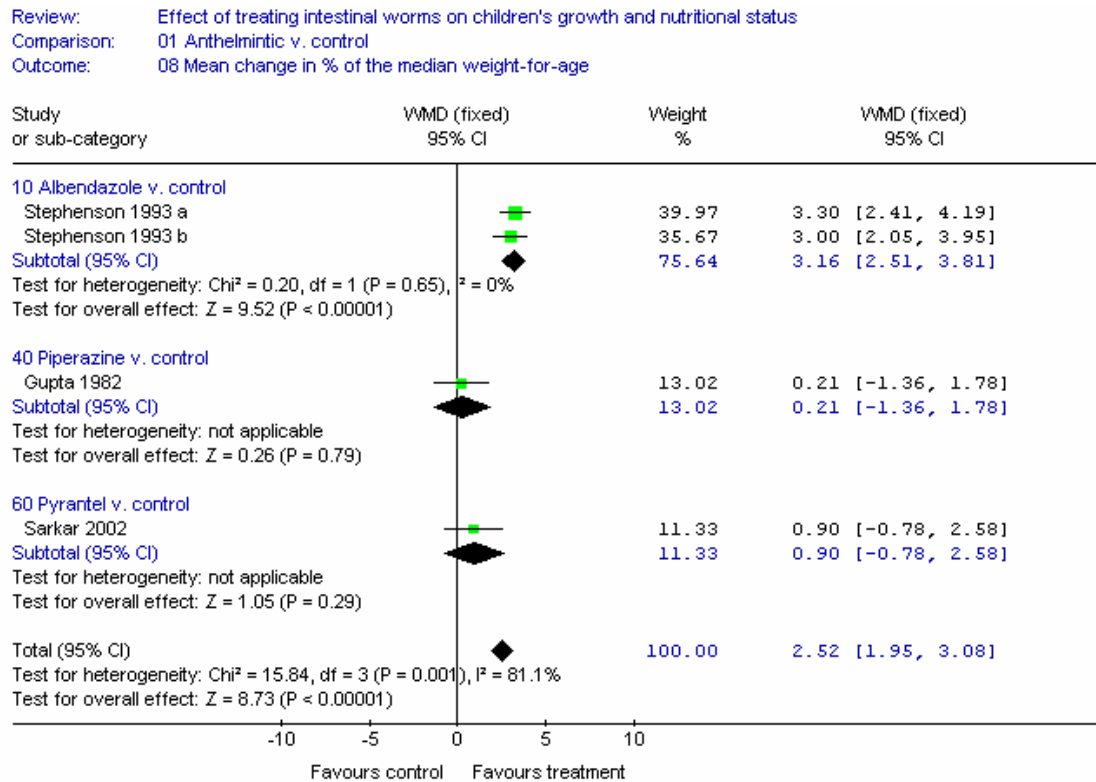


Figure 21. The effects of treating intestinal worms on percentage of the median height-for-age. To interpret the figure, see Section 5.3.

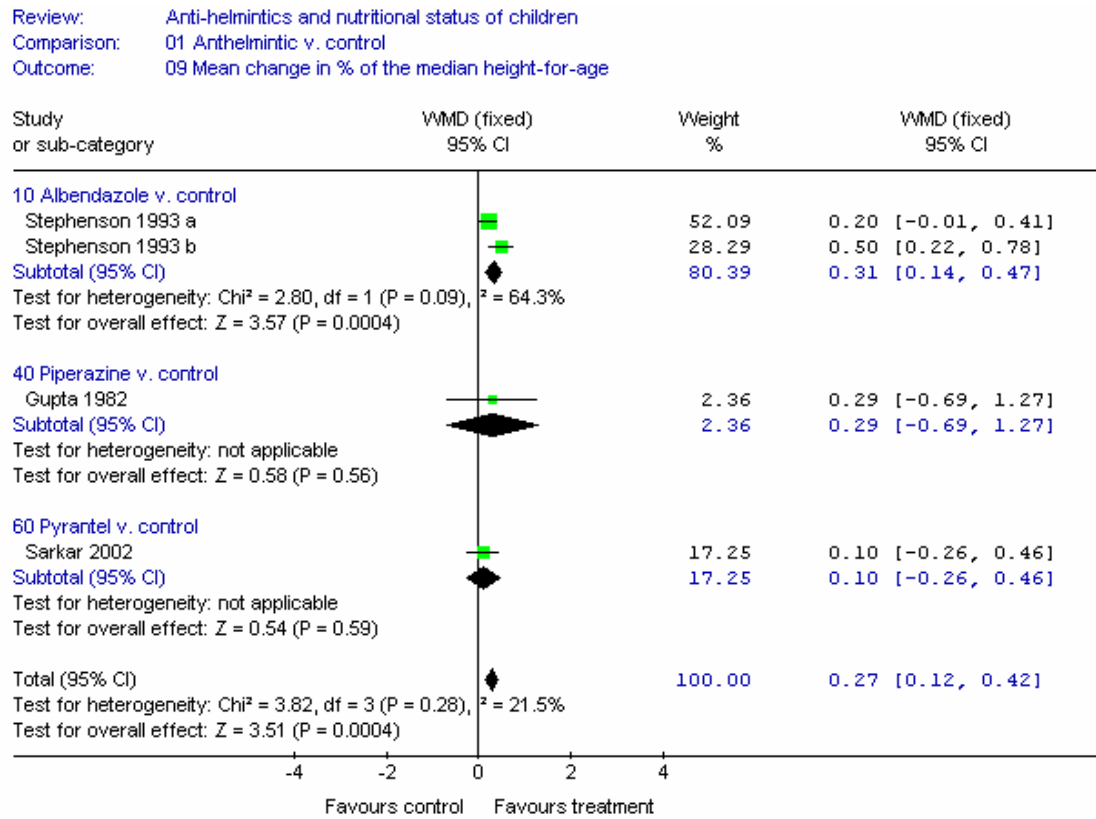


Figure 22. The effects of treating intestinal worms on percentage of the median weight-for-height. To interpret the figure, see Section 5.3.

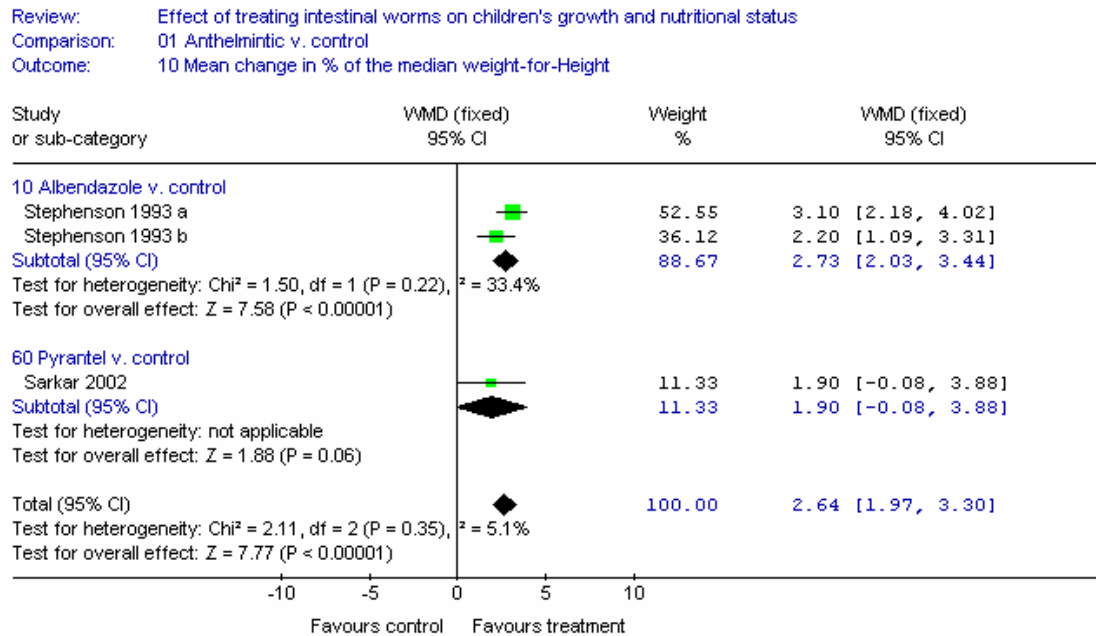


Figure 23. The effects of treating intestinal worms on haemoglobin concentration (g/dL). To interpret the figure, see Section 5.3.

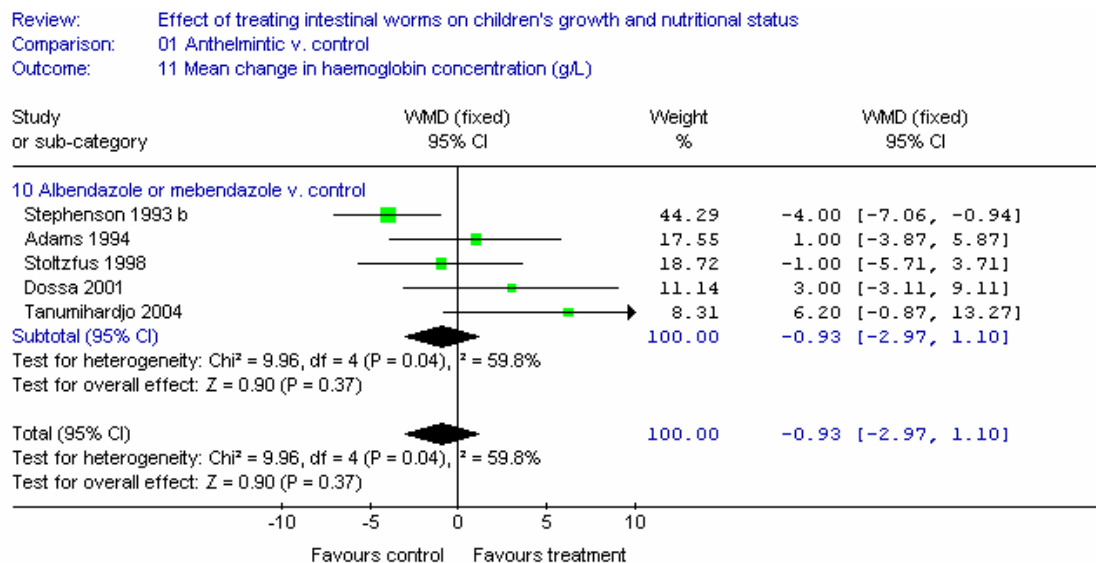


Figure 24. The effects of treating intestinal worms on the dehydroretinol/retinol ratio expressed as a percentage. To interpret the figure, see Section 5.3.

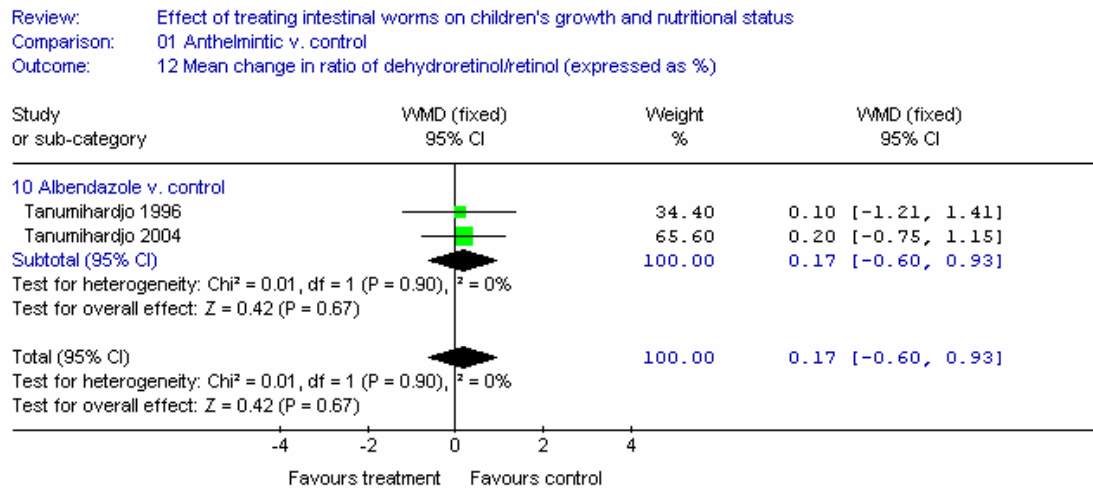


Figure 25. A 2 by 2 factorial design to estimate the effect of deworming with or without a nutritional treatment or not.

		Anthelmintic treatment	
		Yes	No
Nutritional intervention	Yes	A	B
	No	C	D

Figure 26. The costs of anthelmintic treatment per child for a drug costing 3 US cents per child and the costs per infected child treated.

