Treatment and prevention of trichuriasis: efficacy of albendazole in disadvantaged children at Rawsonville Primary School, Western Cape Province, South Africa

by

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Summary

Children in socioeconomically disadvantaged communities in the Western Cape and elsewhere in South Africa are frequently infected by *Trichuris trichiura*. Although albendazole and mebendazole are listed as essential drugs for treatment of humans, it is well known that trichuriasis is relatively refractory to anthelmintic treatment. There are some reports that mebendazole is more effective against *Trichuris* and it is available as generics that are relatively cheap. On the other hand, albendazole is better for hookworm and may have some effect against *Giardia duodenalis*, which is common in the same communities. Moreover, albendazole is used in a deworming programme in KwaZulu-Natal, at a dose of 400 mg *stat*, given once or twice a year depending on the health region in that province.

In terms of diagnosis, infection by intestinal helminthiasis can be determined and monitored by simple, non-invasive, sustainable and cost effective methods. The epidemiological significance of high prevalence extends far beyond the worms *per se* because they are an index of environmental conditions that pose a risk of several other diseases. These include infection by organisms that can cause epidemics of enteric disease. These facts pertain within a deteriorating milieu in terms of human ecology, because the informal sector of the population is burgeoning under dynamic forces that include urbanisation, migration, poverty and disease.

The study reported in this thesis had three main objectives within the context and concepts of the realities described in the previous two paragraphs. The first was to review and consider all information on trichuriasis that could be detected in the literature, and to relate the result to South African needs. The second was to test efficacy of albendazole against trichuriasis in children from a community where it is the predominant worm infection, by means of a well designed and controlled study. Finally, it was

necessary to consider other results associated with treatment. These included possible drug resistance and effects on growth, eosinophilia, iron status and toxicity.

The literature survey established that South Africa lags behind many other developing countries in defining and addressing the problem of helminthiasis as a whole. The conventional epidemiology of trichuriasis as described in the literature is based mainly on studies in the West Indies. Surveys completed recently in the Western Cape Province of South Africa confirm some of the epidemiological concepts, with two notable exceptions. First, the age-related prevalence peaked in children who were 14 years old in a suburb of Cape Town. This is older that in West Indian children. The second difference is probably more important and was detected in children at schools serving the informal sector of Khayelitsha. This is densely populated and the sanitation is often not effective and is sometimes totally lacking. The distribution of egg counts in 316 Khayelitsha children was not overdispersed to low counts, which is perceived as invariably the situation in the West Indies. In the Khayelitsha survey, approximately 25% of children had more than 10 000 eggs per g of faeces.

The randomised controlled treatment trial tested a series of four albendazole treatments, at doses of 400, 800 and 1200 mg (given as 400 mg/day), repeated at intervals of approximately four months in matched groups of children. Results indicate that mass deworming programmes in South Africa should not use albendazole at a dose of 400 mg *stat* for control of infection by *Trichuris trichiura*. The package insert of the product tested (*Zentel*®, SmithKline Beecham) recommends that "in heavy mixed infestation involving *Trichuris*, a single daily dose may be inadequate and the dose may be given for three consecutive days". This statement is not accurate because even when infection by *Trichuris* was not intense, as defined internationally in terms of egg counts per g of faeces, and it was the only helminth present, the cure rate achieved by repeated doses of 400 mg of albendazole was not satisfactory. Moreover, 48% (15/31) of treated children remained continuously infected, although egg counts were clearly reduced. This result demonstrates that continuous use of a dose of 400 mg which is the maximum *stat* dose permitted in South Africa, is likely to facilitate development of true genetic resistance to albendazole by *T. trichiura*. Doses of 800 and 1200 mg were more efficacious and continuous infection reduced to 21% (9/43) and 2.5% (1/39), respectively. A dose of 800 mg for routine use in mass deworming programmes, as 400 mg/day, can be recommended on the basis of sufficiently efficacious treatment, simplification of compliance, and reduction of cost. The frequency of treatment within such programmes should probably be three times per year when prevalence of severe infection exceeds 10% ("severe infection" is defined internationally as an egg count of more that 10 000 per g of faeces). When severe infection is less frequent, treatment could be less often, but more definitive research of this aspect is necessary under local conditions. There was some evidence that incidence increased seasonally during summer and autumn in the community concerned.

A range of other results was recorded. The possibility of genetic resistance to albendazole by *Trichuris trichiura* was not excluded. There was significant reduction of eosinophilia during treatment with albendazole. This may have immunological implications for incidence, prevention and progression of other diseases. Treatment appeared to be beneficial in terms of growth and iron status, but there was not sufficient statistical power to confirm this. No evidence of toxicity at the highest dose (1200 mg given as 400 mg/day for three days) was detected.

Opsomming

Kinders in sosio-ekonomiese agterblewe gemeenskappe in die Wes-Kaap en ook elders in Suid-Afrika toon gereelde infeksies met *Trichuris trichiura*. Albendazool en mebendazool word gelys as noodsaaklike medikasie vir menslike behandeling, maar dit is wel bekend dat *Trichuris* relatief moeilik is om te behandel. Daar word gerapporteer dat mebendazool meer effektief is teen *Trichuris* en maklik beskikbaar is as goedkoper generiese medikasie. Albendazool, aan die ander kant, is effektief teen haakwurm en kan ook 'n effek het teen *Giardia duodenalis*, wat voorkom in dieselfde gemeenskappe. 'n Dosis van 400 mg albendazool, een of twee keer per jaar, word huidelik gebruik in 'n onwurmingsprogram in KwaZulu-Natal. Die frekwensie van behandeling word bepaal deur die gesondheids streek binne die provinsie.

In terme van diagnose, kan infeksie deur intestinale helminte bepaal en gemonitor word deur eenvoudige, nie-invallende, koste effektiewe maniere. Die epidemiologiese betekenis van 'n hoë voorkoms strek verder as net die wurms omdat hulle 'n indeks is van omgewings besoedeling wat kan dui op die risiko van verskeie ander siektes. Dit sluit in infeksies deur organismes wat epidemies van enteriese siektes veroorsaak. Hierdie feite pas binne die agteruitgang in terme van menslike ekologie, want die informele sektor van die bevolking is onder dinamiese druk wat verstedeliking, migrasie armoede en siektes insluit.

Die studie, waarvan verslag gegee word in hierdie tesis, het drie vername objektiewe binne die konteks en konsepte van die realiteite soos beskryf in die vorige twee paragrawe. Die eerste objektief was om alle informasie aangaande trichuriase in die literatuur in oorsig te neem en dit in verband te bring met Suid-Afrikaanse behoeftes. Die tweede was om die werksaamheid van albendazool teen trichuriase te toets in kinders van 'n gemeenskap waar wurm infeksies oorheers, deur middel van 'n goed beplande en gekontroleerde studie. Laastens was dit nodig om ander resultate , geassosieer met behandeling, in

ag te neem. Dit sluit in moontlike weerstand teen die medikasie en die effek op groei, ysterstatus en toksisiteit.

Die literatuur oorsig toon dat Suid-Afrika 'n agterstand het met baie ander ontwikkelende lande om die omslag van die probleem van helminte te bepaal en ook om dit aan te pak. Die konvensionele epidemiologie van trichuriase, soos beskryf in die literatuur, is gegrond op studies in die Wes-Indies. Opnames wat onlangs in die Wes-Kaap gedoen is, bevestig sekere epidemiologiese konsepte met twee vername uitsonderings. Die eerste is die ouderdoms verwante voorkoms wat 'n hoogtepunt bereik in 14 jarige kinders in 'n voorstad van Kaapstad. Dit is ouer as in die Wes-Indiese kinders. Die tweede verskil is miskien meer belangrik en was vasgestel in skool kinders in 'n informele sektor van Khayelitsha. Dit is 'n dig bewoonde area met oneffektiewe of 'n totale gebrek aan sanitasie. Die verspreiding van eier tellings in 316 Khayelitsha kinders was nie oor-versprei tot lae tellings nie, wat andersins die geval in die Wes-Indies was. In die Khayelitsha studie het ongeveer 25% van kinders meer as 10 000 epg stoelgang.

Die gekontrolleerde ewekansigheidstoets soos bespreek in hierdie tesis het 'n reeks van vier albendazool behandelings, by dosisse van 400, 800 en 1200 mg (gegee as 400 mg/dag), herhaal by pouses van ongeveer vier maande in gelyke groepe van kinders, ge-evalueer. Die resultate toon dat massa ontwurmings programme in Suid-Afrika nie die 400 mg dosis vir kontrole van *Trichuris trichiura* moet gebruik nie. Die pakkie insetsel van die produk wat getoets was (*Zentel*®, SmithKline Beecham) dui aan dat in swaar gemengde infeksies waar *Trichuris* betrokke is, 'n enkele dosis onvoldoende is en dat die dosis vir drie agtereenvolgende dae gegee mag word. Hierdie stelling is onakkuraat want al is die infeksie deur *Trichuris* nie swaar nie, soos internasionaal gedefinieer in terme van eier telling per gram stoelgang, en al is dit die enigste intestinale wurm teenwoordig, is die genesingsyfer wat behaal is met herhaalde dossise van 400 mg albendazool nie bevredigend nie. Inteendeel, 48% (15/31) van behandelde kinders was aanhoudend besmet, al was eier tellings duidelik verminder.

Hierdie resultaat wys dat herhaaldelike gebruik van 'n 400 mg dosis, wat die maksimim dosis toelaatbaar in Suid-Afrika is, genetiese weerstand van albendazool deur *Trichuris trichiura* kan fasiliteer. Die 800 mg en 1200 mg dosis was meer doeltreffend en het herhaalde infeksie verminder tot 21% (9/43) en 2.5% (1/39) onderskeidelik. Die 800 mg dosis as 400 mg/dag word aanbeveel vir roetine gebruik in massa ontwurmings programme. Dit is meer doeltreffend, behandeling word vereenvoudig en koste word verminder. Die frekwensie van behandeling binne sulke programme moet waarskynlik drie keer per jaar wees wanneer die prevalensie van swaar infeksies meer as 10% is ("swaar infeksie" word internasionaal gedefinieer, wanneer eier tellings meer as 10 000 eiers per g stoelgang is). As swaar infeksies minder voorkom, kan behandeling minder gereeld wees, maar meer bepaalde navorsing onder plaaslike kondisies is nodig. Daar is sekere bewysse dat insidensie seisoenaal verminder, tydens somer en herfs, in hierdie gemeenskap.

'n Reeks van ander resultate was ook aangeteken. Die moontlikheid van genetiese weerstand van *Trichuris trichiura* teen albendazool word nie uitgesluit nie. Daar was 'n aanmerklike vermindering van eosinophillia tydens behandeling met albendazool. Dit mag immunologiese implikasies vir insidensie, voorkoming en voortgang van ander siektes voorspel. Dit blyk of behandeling groei en yster status bevoordeel het, maar daar was nie genoegsame statistiese mag om dit te bevestig nie. Geen bewys van vergiftiging by die hoogste dosis (1200 mg gegee as 400 mg/dag vir drie dae) is waargeneem nie.

Parts of the research described in this thesis were presented at the following conferences :

The 28th Conference of the Parasitological Society of Southern Africa held at Augrabies Fall National Park, Northern Cape from 19-22 October 1999.

The 29th Conference of the Parasitological Society of Southern Africa held at the University of the Orange Free State, Bloemfontein from 27-29 September 2000.

Publications

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LIST OF ABBREVIATIONS USED

A. lumbricoides	*Ascaris lumbricoides*
AIDS	Acquired immunodeficiency syndrome
AM	arithmetic mean
CR	Cure Rate
epg	egg per gram of stool
ERR	Egg Reduction Rate
g/dl	gram per deciliter
GM	geometric mean
Hb	haemoglobin
HIV	Human immunodeficiency virus
IFN-γ	Gamma Interferon
Il	Interleukin
JT	Jonckheere-Terpstra Statistical Test
km	kilometer
LRM	Linear repeated measures analysis
m	meter
MLN	Mesenteric lymph node
MN	McNemar's chi-squared test
mg	milligram
MRC	South African Medical Research Council
NGO	Non Government Organisation
PSFA	Peninsula School Feeding Association
T. trichiura	*Trichuris trichiura*
TDS	*Trichuris* dysentery syndrome
Th1	T helper 1 lymphocytes
Th2	T helper 2 lymphocytes

Definition of key terms used in this thesis.

Acute

This is a temporal dimension indicating sudden onset and persisting for seconds, minutes or hours. Appendicitis can be an acute complication of trichuriasis, for example. Longer duration becomes subacute and eventually chronic. The relationship to degree can be either way. Pain can be severe and acute, or mild and acute.

Arithmetic mean

In terms of *Trichuris* egg counts, or any other set of measurements, this mean is calculated by dividing the sum of values comprising the series, by the number in the series. It is a valid descriptive statistic for a set of values with a normal (Gaussian) distribution, but **not** for skewed distributions.

Chronic

With regard to disease and pathology, this term means of long duration, such as weeks, months, years, decades or permanently. Trichuriasis is usually a chronic disease (Getz, 1945). Morbidity and severity of chronic disease can range from subclinical to potentially terminal.

Clinical

Disease which requires medical or surgical diagnosis or treatment. The *Trichuris* dysentery syndrome (TDS) is a good example of clinical trichuriasis (Getz, 1945; Mathan & Baker, 1970; Bowie *et al*, 1978; Cooper *et al*, 1986; Cooper & Bundy, 1988; Callender *et al*, 1992; Callender *et al*, 1998).

Cure rate (CR)

The number of *Trichuris* egg positive individuals who are negative after anthelmintic treatment, expressed as percent of the total number of egg positive cases treated. The result must be assessed before new infections become patent in terms of eggs appearing in stools, which is about three months (Beaver *et al*, 1984). This is an important parameter for testing efficacy and for detecting resistance to an anthelmintic previously established as efficacious (WHO, 1998a).

Definitive host

The vertebrate host which harbours the adult or sexual stage of the helminthic parasite eg. *Trichuris trichiura* in the caecum of humans. "Final host" is sometimes used, but since the life cycle is continuous, it is not appropriate.

Egg reduction rate (ERR)

This is the reduction in geometric mean egg count after an anthelmintic treatment, assessed before new infections become patent (see CR). It is expressed as percent. Again it is used to assess efficacy and to check for resistance to anthelmintics known to be efficacious (WHO, 1998a). It is also used to measure effectiveness of mass treatment programmes, which is determined by the combination of an efficacious drug with all elements of delivery, such as treatment compliance, or the failure thereof (Montresor *et al*, 1999).

Endemic

Any disease, including trichuriasis, which is prevalent continuously in a community or population of people. When the prevalence is continuously high, meaning that the disease affects a large proportion of people, the term "hyperendemic" can be used.

Epidemic

The rapid spread of a new disease, or new cases of an endemic disease, through a community or population is an epidemic. When the spread engulfs whole continents, the term pandemic is valid.

Epidemiology

It follows from the definition of epidemic, that epidemiology refers to scientific definition, analysis and documentation of environmental and human factors which cause, are associated with, or characterise epidemics or pandemics. Therefore, epidemiology is a broad discipline in which other disciplines interact.

Geohelminth

Characterised by a life cycle which is initiated with the passage of eggs in the faeces of the definitive host. When stools break down and mix with earth under suitable conditions of temperature and moisture, the eggs undergo embryonation to form L1, L2, L3 or L4 larvae which are the infective stages of nematodes. However, in *Trichuris* spp., the L1 larvae is the infective stage. Infection or re-infection of the definitive host takes place directly by ingestion of mature eggs, without the necessity of an intermediate host or vector. Egg development in earth is obligatory. Examples of geohelminths are *Trichuris trichiura, Ascaris lumbricoides* and the hookworms *Necator americanus* and *Ancylostoma duodenale*.

Geometric mean (GM)

This parameter offers a valid method to normalise skewed data for analysis, such as *Trichuris* egg counts per gram of stool (Anderson, 1986; Bundy *et al*, 1992). A series of egg counts with a negative binomial distribution has a GM that approximates to the median. The GM can be calculated in two ways, either as the n^{th} root of the product of a series of n values, or as the antilog of the mean log of the series. The result is the same. Neither method can handle zero values which must be converted to one for purposes of calculation. This manipulation makes no difference to the result. Alternatively, only positive counts are included.

Incidence

The rate at which new patent infections by *Trichuris trichiura,* or any pathogenic microbe, take place in relation to population and as a function of time. An incidence of 15% per annum means 15 new infections per 100 children per year. Incidence must be measured in children who were not originally infected, because in children with existing infection, the new infections are disguised by existing infection, under normal circumstances.

Infection

The term refers to invasion of the body by pathogenic micro-organisms *in vivo* in man and other animals. The specific meaning for this thesis is parasitism of the human caecum, colon and rectum by adult male and female *Trichuris trichiura* helminths, which may or may not, cause subclinical or clinical disease and/or morbidity. Patent infection by this helminth requires copulation as the prerequisite for production of fertile eggs. In general, the term has a much wider meaning encompassing all pathogens which can cause communicable diseases. Colonisation of the intestinal tract by a normal flora of saprophytes and commensals is not infection. **Infestation** is synonymous with regard to helminths.

Intensity

In the context of this thesis this refers to the number of adult *Trichuris trichiura* present in the intestine. Strictly speaking, this can only be determined at necropsy or by expulsion studies (Bundy *et al*, 1985a; Bundy *et al*, 1985b). In studies of groups or populations it is valid to estimate intensity from mean egg counts per gram of faeces (epg), because this relates directly to the number of adult male and female worms which are copulating. However, for an individual several stools must be sampled to obtain a valid mean egg count, and in turn a realistic estimate of intensity. In this thesis geometric mean (GM) egg counts are used to estimate intensity due to the distribution of counts is characteristically skewed, because of overdispersion or aggregation to low counts in most infected individuals (Anderson, 1986; Bundy *et al*, 1992; Bundy & de Silva, 1998).

Microparasites

Includes viruses, bacteria and protozoa. They reproduce within the host, often at high rates (Maizels, 1993). Microparasitic infections are often acute and short-lived and following recovery, immunity may be protective and even lifelong.

Macroparasites

Includes the helminths that do not multiply within the definitive host, but reproduce sexually to produce transmission stages that egress through faeces and urine (Maizels, 1993). In contrast to microparasites, macroparasites induce long-lasting, chronic infections in which individual organisms persist for years.

Morbidity

This term refers to the whole complex of impaired health and development due to parasitism by *Trichuris*, rather than to symptomatic disease. **The summation of morbidity over large numbers of children is the most important aspect of trichuriasis.** Over whole populations, small impairments can add up to massive problems. For the individual, morbidity ranges from imperceptible, to the *Trichuris* dysentery syndrome (TDS) in young children. TDS incorporates mental impairment that may be permanent, severe retardation of growth, anaemia, chronic colitis, diarrhoea, dysentery, dehydration, rectal prolapse, secondary infection by enteropathogens, persistent abdominal pain and discomfort, and finger clubbing. Although trichuriasis is usually less severe in older children, even adults can be symptomatic (Sandler, 1981), and appendicitis can be a complication (Getz, 1945; Joo *et al*, 1998).

Negative binomial distribution

This is the usual distribution of egg counts per gram of stool for *Trichuris*, and is characterised by severe skewing due to the fact that most infected individuals have low counts and few individuals have very high counts (Anderson, 1986; Bundy *et al*, 1992). Similar meanings are conveyed by **"overdispersed"** or **"highly aggregated"**, with reference to egg counts. Due to skewing, the arithmetic mean is not a valid descriptive statistic of the distribution of helminth egg counts, and cannot be used for statistical analysis. It also bears no resemblance to the median.

Normal or Gaussian distribution

This refers to a distribution of measurements, such as egg counts per gram of stool, in which the arithmetic mean and the median are equal in value, and form the peak or apex of a symmetrical bell-shaped distribution of all measurements ranging between the minimum and maximum for the sample. This type of distribution is **not** characteristic of helminth egg counts, and this has fundamental implications for analysis of data.

Parasite

Any micro or macro-organism which lives on or in a host, which is usually a larger organism that provides physical protection and nourishment (Beaver *et al*, 1984). For example *Trichuris trichiura* is a nematode which inhabits the colon and is associated with chronic dysenteric illness in children (Getz, 1945; Joo *et al*, 1998).

***Trichocephalus trichiura* (dispar)**

This is an old taxonomic name for *Trichuris trichiura*, the helminthic nematode which parasitises humans (Jung & Beaver, 1951; Beaver *et al*, 1984).

CHAPTER 1

Introduction

Over the last decade, intestinal nematode infections have been increasingly recognised as an important and soluble health problem (Bundy, 1990). Soil-transmitted helminthiasis are amongst the most common parasitic infections and can cause malnutrition, anaemia and growth retardation, and are associated with susceptibility to other infections. Bundy & de Silva (1998) suggest that nematode infections still affect more than a quarter of the world's population. Most of those chronically infected by intestinal parasites live in developing countries (Bundy *et al*, 1992; Bundy & de Silva, 1998). It has been suggested that the global burden of disease from geohelminthiasis may be significantly greater than was supposed from estimates of prevalence because several tens of millions of children are likely to suffer permanent developmental consequences (Chan *et al*, 1994). School children harbour the most intense infections with the commonest worms (Bundy & de Silva, 1998). The UNESCO initiative to give children an opportunity to derive maximum benefit from the schooling they receive, recognises the fact that poor nutrition and health secondary to helminthiasis, can severely affect a child's ability to learn (Halloran *et al*, 1989).

The major soil-transmitted helminths are *Trichuris trichiura* (whipworm), *Ascaris lumbricoides* (roundworm), and the hookworms *Ancylostoma duodenale* and *Necator americanus*. They often occur together in the same geographical areas and even in the same person (Stephenson *et al*, 1989). Recent information indicates that more than 900 million people worldwide are infected by *T. trichiura* (Bundy & Peto, 1998). *Trichuris* dates back to the Ice Age. In September 1991, a well preserved mummy was found in a glacier in the Ötztal Alps at an altitude of 3200m on Italian territory less than 100m from the

Austrian border. It turned out to be the body of a 25-30 year old man who had died about 5 200-5 300 years ago. Samples from the colon of this mummy showed numerous *Trichuris* eggs (Aspöck *et al*, 1996). Identifiable ova have also been recovered from coprolites, dating back 2 000 years, in prehistoric salt mines in Austria (Bundy & Cooper, 1989). The most recent report documents the discovery of a coprolite, containing three *Trichuris* eggs, from a late stone-age man (10 000-7 000 years before present) recovered from Kruger cave, in the Magaliesberg mountain range in South Africa (Evans *et al*, 1996).

Trichuris infestation has been considered by some paediatricians as a relatively benign condition (Jung & Beaver, 1951) producing symptoms and physical signs only when present in large numbers. However, it was confirmed in 1998 that even symptomless trichuriasis impaired growth of children (Forrester *et al*, 1998). Studies have also showed that children infected with whipworm showed increased growth after being treated indicating that a relationship between growth and infection does exist (Gilman *et al*, 1983; Cooper *et al*, 1990; Callender *et al*, 1994; Stoltzfus *et al*, 1997; Hadju *et al*, 1998). There is a negative correlation between helminth infections in children and school attendance, school performance or other tests of cognitive performance (Nokes & Bundy, 1994). Simeon *et al* (1994) examined the relationship between varying intensities of infection and school achievement and found that uninfected children had higher reading and arithmetic scores than children with infections of 4000 epg (intensity of infection is expressed as numbers of eggs per gram of faeces, WHO, 1996). They were also taller than those with intensities greater than 2000 epg. Children with mild to moderate infections of *Trichuris* (>2000 epg) improved in three of eight cognitive tests, after anthelmintic treatment (Nokes *et al*, 1992).

Heavy infections with *Trichuris* can cause *Trichuris* dysentery syndrome (TDS), characterised by colitis (inflammation of the colon), anaemia, severe stunting, diarrhoea, dysentery, finger clubbing and rectal prolapse (Getz, 1945; Jung & Beaver, 1951; Bowie, 1978; Cooper *et al*, 1986; Cooper & Bundy, 1988;

Cooper *et al*, 1990; Callender *et al*, 1998). In community studies done in the West Indies where prevalence of trichuriasis among children aged six months to six years was 84%, more than 4% of those over two years had rectal prolapse, as illustrated in Fig. 1 (Cooper & Bundy, 1988).

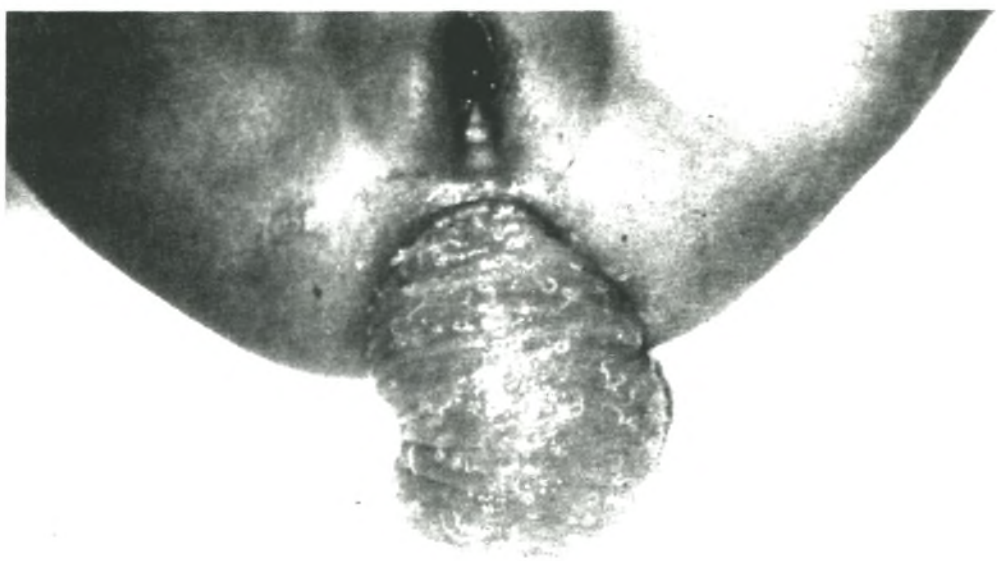

Fig.1: Numerous adult *Trichuris* worms are the white objects attached to the mucosa of a prolapsed rectum of a two year old child (from Beaver *et al*, 1984).

There seems to be a relationship between severe trichuriasis, including TDS, and anaemia; with anaemia improving after anthelmintic treatment (Callender *et al*, 1994; Ramdath *et al*, 1995; Karyadi *et al*, 1996; Kruger *et al*, 1996; Hutchinson, 1997; Stoltzfus *et al*, 1997; Hadju *et al*, 1998). The pathogenesis of anaemia in trichuriasis is due to leakage of red blood cells through mucosal inflammation and not to frank haemorrhage (Neafie & Connor, 1976). The leakage is a net loss of iron because the haemoglobin cannot be digested, as it can be in the case of haemorrhage due to hookworm. Hypochromic anaemia, which is seen in cases with prolonged massive infection is due to the combination of general malnutrition and blood loss from the friable colon and prolapsed rectum and not directly to the extraction of blood from the host by the parasite (Jung & Beaver, 1951; Layrisse *et al*, 1967; Neafie & Connor, 1976; Beaver *et al*, 1984).

Adult *Trichuris* worms attach to the mucosa of the cecum and the colon, where their anterior portions penetrate beneath the epithelium and cause colitis (Neafie & Connor, 1976). In some cases the appendix may be involved and patients may present with features of acute appendicitis. Sixteen out of 20 patients with appendicitis showed the presence of *Trichuris* in a study done by Getz (1945). When many adult worms are present in the appendix, the associated inflammation and granulomata can obstruct the lumen and arouse symptoms of appendicitis.

In South Africa, urbanization has occurred into unserviced, informal settlements and more than 80% of the population is socio-economically disadvantaged. Under these circumstances, little is known about the dynamic epidemiology of human intestinal parasitic infections in South Africa and the national literature on helminth infections is mostly retrospective, descriptive and fragmented (Fincham *et al*, 1996).

Infection of South African children by worms has been confirmed repeatedly (Burger, 1968; Van Niekerk, 1979; Gunders *et al*, 1993; Bradley & Buch, 1994; Fincham *et al*, 1996). Prior to the first democratic elections in 1994, the problem of intestinal parasitic infections were not directly addressed. This country has lagged far behind other developing countries on this issue. Surveys conducted since 1996 in the Western Cape Province have confirmed real problems in terms of prevalence and variable intensity, particularly of trichuriasis (Table 1; Author's unpublished data). Informal settlements are characterised by overcrowding of people living in unserviced shacks (Figs 2 & 3). In some areas, there are no toilets or sanitation of any kind and drainage is usually inadequate. Because of this, there is often widespread environmental pollution by human faeces, to the extent that children have no option but to play in places that are also used as toilets (Fig. 4).

Table 1 : Surveys of prevalence and intensity of trichuriasis in primary school children in the Western Cape, conducted since August 1996.

Community	**No. of children**	***Prevalence (%)**	***Intensity (epg)**	
			***AM**	***GM**
Langebaan North, 1996	238	73	1078	45
Rawsonville, 1997	462	69	671	41
Khayelitsha, Nolungile, 1997	316	84	12536	1566
Khayelitsha, Site C, February 1999	459	92	733	201
Khayelitsha, Site B, May 1999	492	78	900	96
Ravensmead, 1999	2128	59	224	7
Uitsig, 1999	1939	56	444	15
Mitchells Plain, 1999	50	12	3	1

* See definitions. AM = Arithmetic mean. GM = Geometric mean

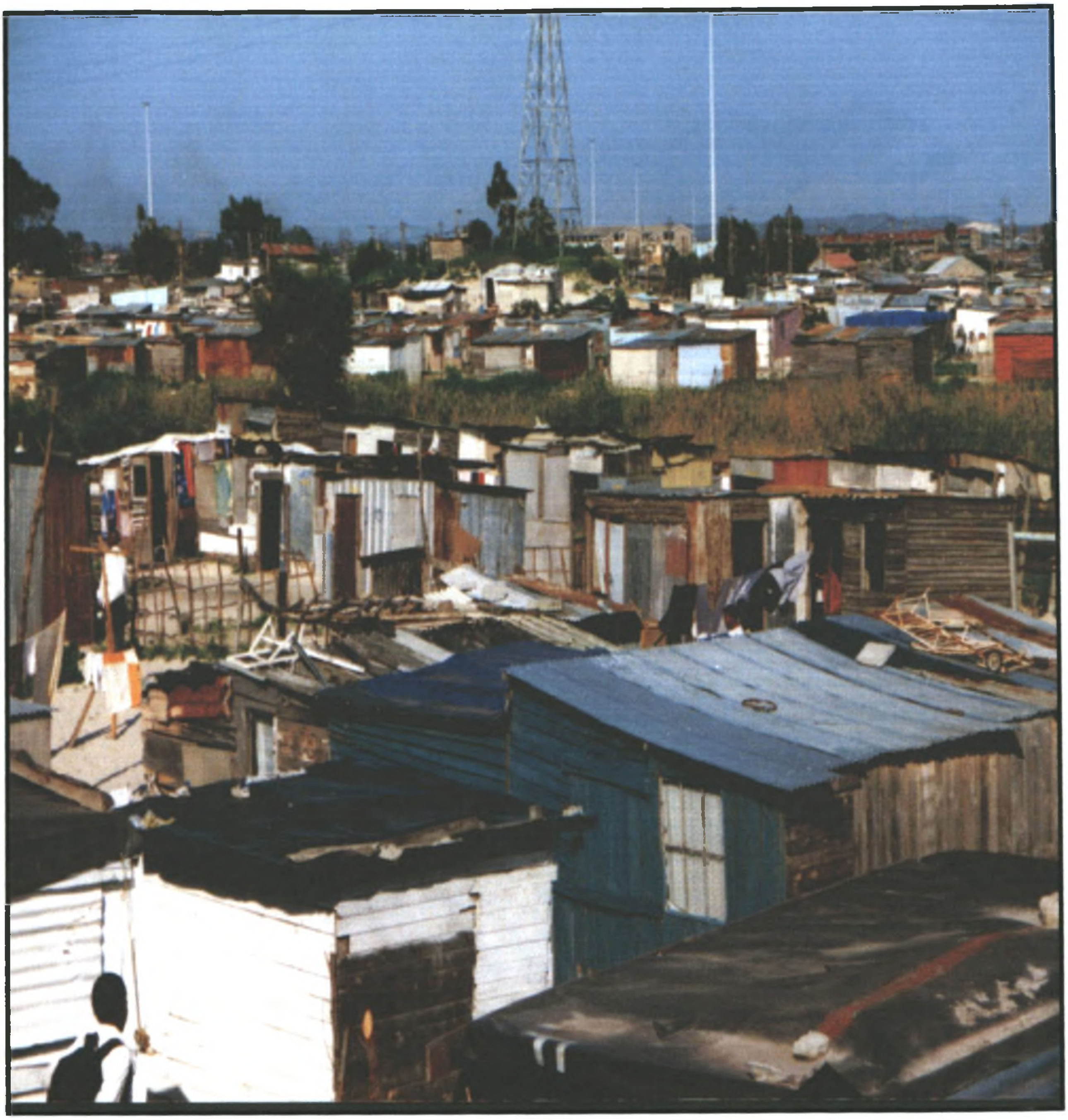

Fig. 2: A large proportion of the South African population are crowded into shacks such as these, or small houses placed close together. Similar situations are frequent in other African, Asian and Latin American countries (Photo: Allan Jefthas, MRC, 1999).

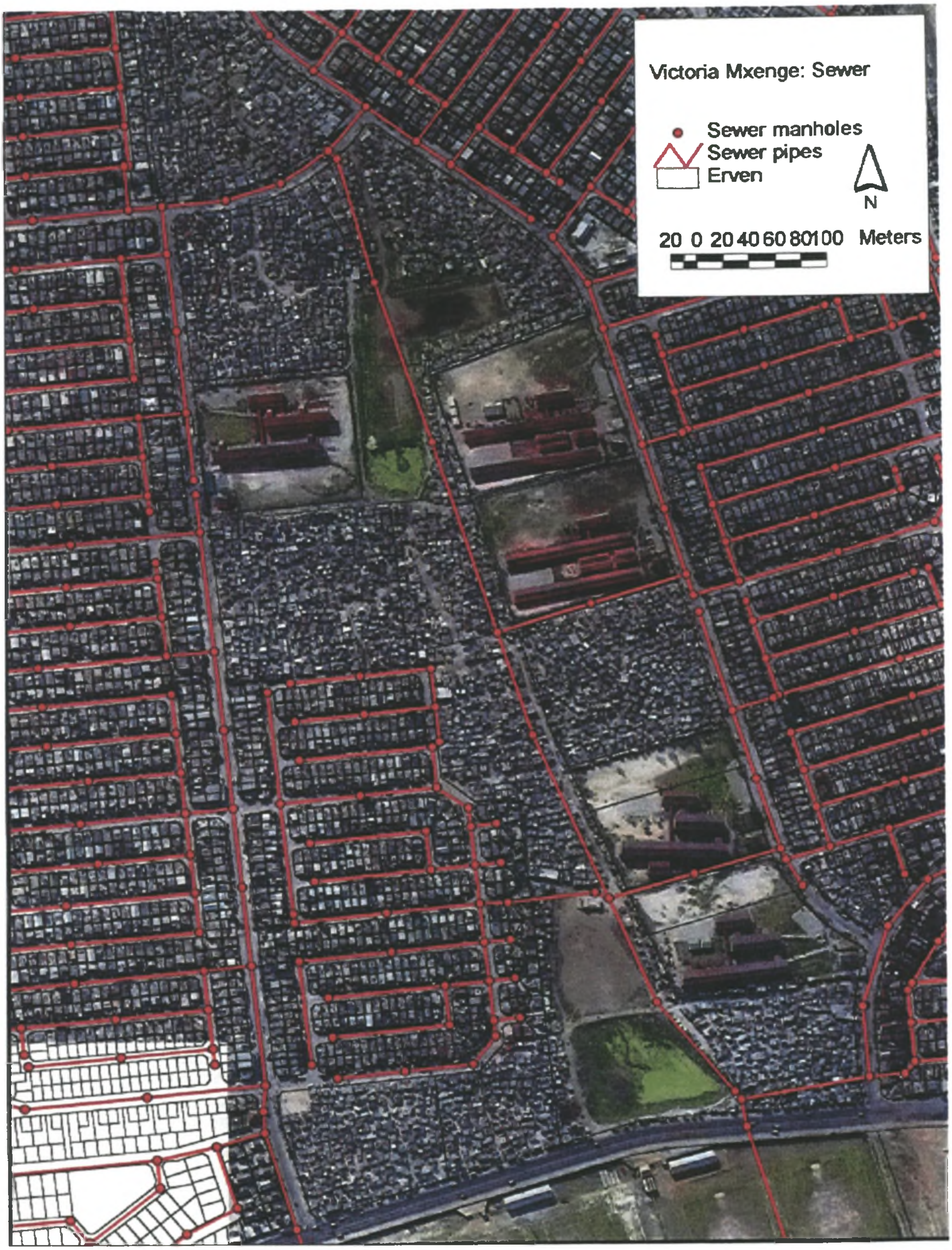

Fig. 3: The aerial photograph taken in 1999 shows why intestinal parasites, and other forms of enteric disease, are a major health risk to many communities in South Africa (City of Tygerberg, Planning Dept). In many of the places where people live in shacks, there is no sanitation.

Fig. 4: Human faeces litter the surface of this public, open air toilet in Khayelitsha, which is also a playground. The arrows in the foreground of the photograph mark discernible stools, but many others have disintegrated and mixed with soil.

Currently the health services are undergoing restructuring and reorientation and are hampered by shortages of both staff and funds. Coupled with this, epidemics of infection by the human immunodeficiency virus (HIV), the acquired immunodeficiency syndrome (AIDS) and tuberculosis (TB) have reached shocking proportions (Bentwich *et al*, 1999; Matchaba, 1999). Elsewhere in Africa, HIV/AIDS has brought despair to large numbers of people, affecting every section of society. HIV seroprevalence figures are overwhelming, with over a quarter of pregnant women infected with the virus (Chintu & Mwinga, 1999). According to the latest UNAIDS report, South Africa has the world's fastest growing HIV/AIDS epidemic with more than 1500 people infected every day (Baleta, 1999). The despair of HIV/AIDS is increased because an ominous increase in TB has followed in its' wake. The importance of the interaction between TB and HIV is now internationally recognised (Elliot *et al*, 1993; Adams *et al*, 1999). South Africa is currently facing one of the worst TB epidemics in the world with disease rates up to 60 times higher that those seen in the United States of America or Western Europe (Fourie & Weyer, 1997; Adams *et al*,1999; Bentwich *et al*, 1999). Estimates by the MRCs' National Tuberculosis Research Programme put the expected burden of TB in South Africa for the year 2000 at 273 365 new cases, of whom 113 945 will be infectious and 46.7% will be HIV positive (Fourie & Weyer, 2000). Efforts to fight these epidemics are consuming most of the human, financial and material resources of the health services. Other essential child health service and delivery, including deworming programmes, is seriously impaired.

This situation means that the only way to deliver anthelmintic interventions is to mobilise communities into an effective partnership with private enterprise, non-government organisations and education. For instance, the current South African health service protocols theoretically provide anthelmintic treatment at the same clinics where people suffering from HIV/AIDS and tuberculosis also come for diagnosis and treatment. It is **not** right to direct a child for deworming into an environment of people with serious contagious and infectious diseases. It is also not in the nature of children who harbour the major burden of geohelminth infections in any community (Bundy & de Silva, 1998; Montresor *et al*, 1998; Montresor *et al*, 1999) to present themselves regularly at clinics for treatment. Clearly the current health policy regarding anthelmintic treatment at clinics does not address the problem satisfactorily. Vaccination programmes for school-age children are implemented at schools and have been highly successful. The same principle could apply to mass deworming programmes. Such programmes have been operating successfully for years in several developing countries (Renganathan *et al*, 1995; Montresor *et al*, 1999). Theory and practice indicate that targeting treatment at school children reduces infection levels in the community as a whole, and the fact that children assemble daily in one place, the school, provides an opportunity to deliver mass treatments through existing infrastructure (Stoltzfus *et al*, 1997; Bundy & de Silva, 1998; Montresor *et al*, 1998; Montresor *et al*, 1999). Delivery of chemotherapy via schools have been shown to be practical and cost effective (Halloran *et al*, 1989; Bundy & de Silva, 1998).

Anthelmintics are less efficacious against *Trichuris* than against *Ascaris* and hookworm (Bundy *et al*, 1985b; Bundy *et al*, 1987; Cooper & Bundy, 1988; Bundy & Cooper, 1989; Chan e*t al*, 1994; Hall & Nahar, 1994; Forrester *et al*, 1998; Jackson *et al*, 1998). Since *Trichuris* is the predominant helminth in the Western Cape (Table 1) and other parts of South Africa (Jackson, 1998), it is particularly necessary to test and monitor efficacy of anthelmintics under local conditions. There is a lack of reliable information on the efficacy and effectiveness of treatment in South Africa, and a need for definitive research. It is also necessary to conduct drug trials to check on development of resistance, because the existence of drug-resistant populations of soil-transmitted nematodes is commonly reported in veterinary literature. There is understandable concern that this problem is a threat to the use of anthelmintic drugs for the control of soil-transmitted nematodes in humans (Montresor *et al*, 1998). For example, *Schistosoma mansoni* is resistant to oxamniquine in Brazil (WHO, 1998b).

The use of a single dose broad-spectrum anthelmintic in mass treatment of helminthiasis is more effective because it increases compliance and simplifies administration and management of a programme (Ow-Yang & Hanjeet, 1986; Montresor *et al,* 1999). However single doses of 400 mg albendazole and 500 mg mebendazole, as recommended by WHO, may not achieve a complete cure, especially with heavy infections of *Trichuris* (Kan, 1982; Hall & Nahar, 1994; Bundy & de Silva, 1998; Bennet & Guyatt, 2000). A comprehensive example of the ineffectiveness of a single dose regimen for the treatment of *Trichuris* is provided by Hall & Nahar (1994) in a study done in Bangladesh. Children who were intensely infected with *Trichuris* were treated with albendazole at doses of one x 600 mg, one x 800 mg, three x 400 mg and five x 400 mg. Repeated doses were on successive days. The single doses achieved only 30% cure rates, and three x 400 mg was needed to achieve a cure rate of 80%. Similar results were also reported by Ow-Yang & Hanjeet (1986). In a South African study, 400 mg of albendazole repeated after six months did not reduce prevalence of *Trichuris* significantly (Kruger *et al*, 1996).

Little consideration has been given to the fact that helminthic infection is the main cause of eosinophilia in developing countries (Rothenberg, 1998). Eosinophils can selectively accumulate in blood and any tissue or body fluid. These concentrations are of clinical and pathological importance because in response to activation, unique cytotoxins and mediators of inflammation stored in cytoplasmic granules are released and augmented by synthesis (Maizels, 1993; Pritchard e*t al*, 1997; Rothenberg, 1998). The human immune response to *Trichuris* has been studied in only a rudimentary way (Bundy *et al*, 1991; Cooper *et al*, 1991; Lillywhite *et al*, 1991; Bundy *et al*, 1992; Needham *et al*, 1992; Needham *et al*, 1993) and it was shown that there is a major response to the parasite that is diverse both at the level of isotype and antibody specificities. Else & Grencis (1991) in work on mouse trichuriasis showed that infection with *T. muris* can polarise the helper T-lymphocyte response towards either the Th1 or Th2 lymphocytes subsets with dramatic consequences for the outcome of infection. The *T. muris* mouse model strongly supports the concept that a Th2-type response is important in resistance to intestinal nematode parasites (Fig. 5).

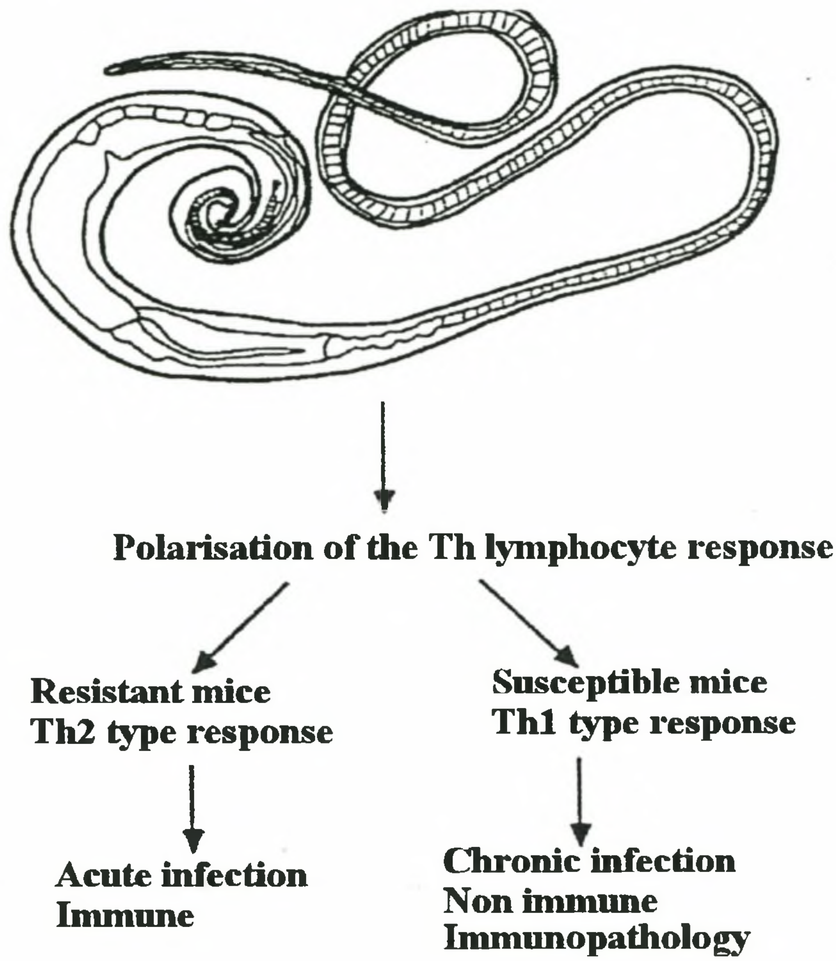

Fig. 5: Polarisation of the helper T-lymphocyte response to *Trichuris* in mice. In resistant mice, acute infection is followed by immunity (Th2). In susceptible mice there is no immunity and infection is chronic (Th1) (from Else & Grencis, 1991).

T-lymphocytes play a central role in immunity to *Trichuris*. During the first exposure, T-cells are primed in mesenteric lymph node (MLN). They then migrate to the site of infection where, as effector cells, they encounter parasite-derived antigens and secrete the cytokines characteristic of the helper T-cell subset to which they have become committed. In resistant strains of mice, expulsion of *T.muris* is associated with the activation of helper T-cells within the MLN that are capable of secreting IL-4, IL-5 and IL-9, and the absence of gamma interferon (IFN-γ). This is a characteristic Th2 response. In strains of mouse unable to expel the parasite, a chronic infection develops and IFN-γ producing Th1 cells predominate with little evidence of a Th2-type response.

It is possible that humans predisposed to heavy infections of *T. trichiura* are responding to infection in an inappropriate fashion and reacquire heavy worm burdens after drug intervention partly because of immunological memory of the wrong type of immune response. Alternatively the majority of people harbouring smaller worm burdens may be able to mount an appropriate immune response. Africans at risk of infection by HIV are often infected by parasitic helminths. This phenomenon seems to span the whole African continent. A community in Addis Ababa, at one end of the African continent, showed a helminth prevalence of 86% (Nahmias *et al*, 1983) and children in primary schools near Cape Town, at the opposite end of the continent showed prevalences of between 80-100% (Fincham *et al*, 1999).

CHAPTER 2

Review and Comparative Analysis of Literature

In this chapter published papers which report on studies, trials, reviews, descriptive surveys and research letters that describe results on *Trichuris*, are summarised in Table 2. Analysis of these publications by country is presented in Table 3. Distribution of literature by study design is analysed and recorded in Table 4.

The study designs reported on in the context of this thesis are the following :

Randomised placebo controlled trial : A clinical trial that involves at least one test treatment and one control group, concurrent enrollment and follow-up of the test and control treated groups, and in which the participants and treatments are linked as a result of a random process. The control group are given a placebo which is a dummy medical treatment, with no defined pharmacological activity, so that the effects specific to the pharmacological treatment can be distinguished from other non-specific events. Placebo should be identical to the medication under test in appearance, taste, smell and packaging. Participants are not aware of which form of medication they receive, and research staff also do not know. This is called "double blinding".

Randomised controlled trial: No placebo is used, usually for an ethical reason, for example permission to give placebo to Mexican children known to have worms was refused (Forrester *et al*, 1998). In other respects the design is the same as when placebo is used, i.e participants are allocated to different treatments at random.

Case controlled study: A study which starts with the identification of persons with a disease or condition and matched controls without the disease. The matching is for variables like age, gender, community, school, household and socio-economic status, so that the only discernible difference is the disease or condition. This enables definition of effects due to disease.

Clinical trial: A medical trial in which volunteers are treated with a drug, a diet or nutrient, physiotherapy or psychotherapy. Each study is designed to answer clinical or medical questions in a scientific way, for instance does a new medication cure malaria or tuberculosis in a large series of patients. Or to what extent does a new anthelmintic, or a particular dose of an anthelmintic, cure or reduce worm burdens or egg counts.

Reviews: A report which attempts to summarise all known scientific information about any subject, such as an infectious or metabolic disease, or the epidemiology of a helminth parasite.

Cross-sectional study: A survey in which the presence or absence of disease or other health-related conditions is determined in each member of a study population or in a representative sample at one particular time, and the results are described. Examples are descriptions of prevalences and intensity of helminthiasis/trichuriasis at a particular time or date.

Case report: A report of the clinical and pathological data during progression and/or treatment of a person affected by a disease.

Prospective follow-up studies: Longitudinal monitoring in which individuals or populations are followed from a baseline, to assess the outcome of disease, exposure, treatment or management, over time.

Mathematical epidemiology of helminthiasis: Studies which attempt to analyse the overdispersed, highly aggregated distribution of prevalence and intensity of infection by *Trichuris* and other helminths, in hosts. Analysis is by means of mathematics and statistics, in an attempt to define functions and formulae which explain or predict incidence, prevalence and morbidity. Some of these papers seek to define genetic factors in parasites and hosts, which influence resistance and susceptibility. It also includes mathematical analysis of the distribution of helminthiasis in relation to climate and topography, and the calculation of cure rates and egg reduction rates.

Operational research: These studies report on the success or failure of the development and operation of health delivery systems for implementing preventative and therapeutic anthelmintic interventions.

Table 2 : Summary of studies and trials done on *Trichuris* (see list of abbreviations on page vii).

Country	Study design and sample size	Descriptive measures or hypothesis	Results, comments and conclusions	Reference
		RANDOMISED, PLACEBO CONTROLLED TRIALS AND RANDOMISED CONTROLLED TRIALS		
Kenya	**Randomised placebo controlled trial**. 78 children receiving a single 400 mg albendazole dose and 72 children receiving placebo.	Effect of treatment on growth and reduction of epg.	ERR = 28% for *Trichuris* after 6 months. Placebo had no significant effect on the egg count. Decrease in intensity of infections significantly predicted growth improvement. *Ascaris lumbricoides* was also analysed.	Stephenson *et al*, 1989
Thailand	**Randomised placebo controlled trial** 130 children received 400 mg albendazole once per day for 3 days, 30 received 100 mg mebendazole twice daily for 3 days, 30 received placebo once daily for 3 days.	Efficacy of albendazole and mebendazole in relation to intensity of infection by *Trichuris* and number of expelled worms.	Multiple doses of albendazole is less effective than multiple doses of mebendazole when assessed by egg counts, but by actual expelled worm counts multiple doses of albendazole is more effective than mebendazole. Further studies are needed to confirm this phenomena and to determine whether assessing cure rate by egg count only, is an appropriate tool.	Anantaphruti *et al*, 1992
West Indies	**Randomised placebo controlled trial, double blind**. 103 children >2000 epg randomly assigned treatment with 3x400 mg doses of albendazole. 56 children treated with placebo.	Mental development before and after deworming.	In three cognitive tests, children who received treatment improved significantly more than those who received placebo ($p<0.05$). On completion of the study the treatment group and uninfected controls no longer differed significantly. Moderate to heavy infection >2000epg does have a detrimental and reversible impact on a child's cognitive function and there is a need to determine whether the effect of infection on cognitive function has long-term implications for school achievement.	Nokes & Bundy, 1992

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Country	Study design and sample size	Descriptive measures or hypothesis	Results, comments and conclusions	Reference
Thailand	**Randomised placebo controlled trial.** The efficacy of 300 mg polymorph A, 300 mg polymorph C and 500 mg polymorph C mebendazole was tested on 958 primary school children.	The children were randomly allocated in seven treatment groups including the placebo control and the standard dose control (100 mg polymorph C bid for 3 days).	The ERR and CR of 300 mg and 500 mg polymorph C were similar, but inferior to those of the standard dose in both hookworm and *Trichuris* infections. The efficacy of single dose 300 mg polymorph A was not different from that of the placebo control in both infections.	Charoenlarp *et al*, 1993
Thailand	**Randomised controlled trial.** 196 children were randomised into 4 different treatment groups: 1. Single 300 mg mebendazole dose (locally produced). 2. Single 300 mg mebendazole dose (original). 3. Single 500 mg mebendazole dose (original). 4. Single 400 mg albendazole dose (original).	Cure rate (CR) and egg reduction rate (ERR).	For *T. trichiura* : Group 1; CR = 0%, ERR = 28.3% Group 2; CR = 43.3%, ERR = 77.9% Group 3; CR = 70.3%, ERR = 89.9% Group 4; CR = 67.4%, ERR = 87% Both mebendazole and albendazole are safe and no side effects were observed. The results of this study suggested that albendazole is the preferred benzimidazole derivative for mass treatment of **multiple infections** with *Ascaris*, hookworm and *Trichuris*. Local mebendazole was inferior.	Jongsuksuntigul *et al*, 1993
Kenya	**Randomised placebo controlled trial.** Placebo = 93 children. 600 mg albendazole group = 96 children. 1200 mg albendazole group = 95 children.	Growth in infected children given 600 mg albendazole or 1200 mg albendazole per school year.	The 600 mg and 1200 mg groups gained significantly more in weight than the placebo group. ERR for *T. trichiura* was 42% and 32%, respectively. One or two doses of albendazole per year resulted in similar growth improvements, despite re-infection in school-age children.	Stephenson *et al*, 1993a

Table 2 : Summary of studies and trials done on *Trichuris* (see list of abbreviations on page vii).

Country	Study design and sample size	Descriptive measures or hypothesis	Results, comments and conclusions	Reference
Kenya	**Randomised placebo controlled trial.** Placebo = 26 children. Albendazole = 27 children.	Effect of deworming on physical fitness, growth and appetite, in children infected by *T. trichiura*, *A. lumbricoides* and hookworm.	Four months after treatment, the albendazole group showed highly significant improvements in fitness, weight gain and appetite. Single-dose treatment with albendazole can allow improved physical fitness, growth and appetite in school-age children in areas where these helminths and poor growth are highly prevalent.	Stephenson *et al*, 1993b
Tanzania	**Randomised single blind controlled trial.** 2294 children aged 6-12 years.	Efficacy of single dose treatments with 500 mg mebendazole and 400 mg albendazole against intestinal nematodes *T. trichiura, A. lumbricoides* and hookworm.	CR for *Trichuris* were low, but mebendazole was significantly better than albendazole and produced a greater ERR; ERR : albendazole 73.3% ERR : mebendazole 81.6%	Albonico *et al*, 1994
West Indies	**Randomised, placebo controlled trial .** 407 children aged 6-12 years. Randomly assigned to receive albendazole or placebo.	Growth, reading, spelling, arithmetic, school attendance in children infected by *T. trichiura*.	Significant interactions with spelling, body mass index, stunting and school attendance. No significant main effects.	Simeon *et al*, 1995

Table 2 : Summary of studies and trials done on *Trichuris* (see list of abbreviations on page vii).

Country	Study design and sample size	Descriptive measures or hypothesis	Results, comments and conclusions	Reference
South Africa	**Randomised controlled trial**. 65 children from each of 5 primary schools were randomly selected. The subjects in each school were randomly assigned to 1 of 2 groups; 1 received anthelmintic treatment (2 x 200 mg albendazole) and the other placebo. The treatment groups also received iron-fortified soup and anthelmintic treatment, iron fortified soup and placebo, unfortified soup and anthelmintic treatment and unfortified soup and placebo.	Effects of iron fortification and anthelmintic treatment.	Significant effects of anthelmintic therapy on haemoglobin concentrations and height for age z-scores, over and above that achieved by iron fortification/supplementation alone.	Kruger *et al*, 1996
Guatemala	**Randomised double blind placebo controlled trial**. 246 children randomly assigned to receive 400 mg albendazole or placebo at 0 and 12 weeks.	Effects of deworming on school performance indicators in children infected with *T. trichiura* and *A. lumbricoides*.	A high worm burden of *Trichuris* was associated with poorer performance in reading. Limited effect of albendazole against *Trichuris* at dosage used. Geometric mean egg count reduced from 293 to 128 after 24 weeks. Due to the limited effectiveness of a single 400 mg dose of albendazole against *Trichuris*, this study did not provide evidence that successful treatment of *Trichuris* may improve schooling results.	Watkins *et al*, 1996

Table 2 : Summary of studies and trials done on *Trichuris* (see list of abbreviations on page vii).

Country	Study design and sample size	Descriptive measures or hypothesis	Results, comments and conclusions	Reference
Indonesia	**Randomised placebo controlled trial**. 330 children infected with *T. trichiura* and *A. lumbricoides* receiving single doses of either pyrantel, albendazole or placebo at baseline and again at 6months.	Re-examined after treatment at 0, 3, 6 and 12 months.	Reduction of *Trichuris* infection associated with an increased mid-arm circumference. All groups reduced the prevalence and intensity towards the end of the study ($p<0.05$). Treatment of helminth infections in school-age children may improve growth in areas where malnutrition and helminth infections are prevalent.	Hadju *et al*, 1997
Mexico	**Randomised controlled trial.** 622 children infected with *T. trichiura* (with or without other helminths) were randomly allocated to one of 3 treatment regimens; 400 mg albendazole daily for 3 days; 400 mg albendazole once; single dose of pyrantel 11 mg/kg.	Does symptomless *Trichuris* infection impair growth of children? Does a multiple dose regimen of albendazole enhance improvement of growth?	Growth is impaired by symptomless trichuriasis. 1200 mg albendazole did not improve growth in height compared to 400 mg, in children with high egg counts. Hypothesised that 1200 mg might be toxic.	Forrester *et al*, 1998

Table 2 : Summary of studies and trials done on *Trichuris* (see list of abbreviations on page vii).

Country	Study design and sample size	Descriptive measures or hypothesis	Results, comments and conclusions	Reference
Indonesia	**Randomised placebo controlled trial**. 86 boys infected with *T. trichiura* and *A. lumbricoides* receiving single 400 mg dose of albendazole; 43 receiving placebo.	Effect of deworming on growth , appetite and activity.	Six months after treatment, the prevalence of *Trichuris* infections did not change significantly for both groups, but treatment with albendazole significantly reduced intensity of infection. Increases in mid-arm circumference and height-for- age after treatment, in the albendazole group were significantly greater than in the placebo group. Free play activity after treatment, increased by 28% in the albendazole group and did not change in the placebo group. Treatment with single dose of 400 mg albendazole may improve growth, appetite and activity in areas with a high transmission of helminth infections.	Hadju *et al*, 1998
South Africa	**Randomised controlled trial**. 42 children receiving single 500 mg mebendazole and 40 receiving single 400 mg albendazole. Children were all infected with *T. trichiura*.	Prevalence and intensity of infection by *Trichuris*.	Of the mebendazole group, 85% showed a reduction in *Trichuris* epg, compared to the 75% that received albendazole. Mebendazole treatment was associated with a median percentage reduction in ova count of 72.2% which significantly exceeded the 44.1% reduction of albendazole.	Jackson *et al*, 1998
Tanzania	**Randomised controlled trial** Control = 1002 children. Twice yearly deworming = 952 children. Thrice yearly deworming = 970 children. Dose = 500 mg generic mebendazole	The effects of a school-based deworming programme on the iron status of primary school children who were infected by *T. trichiura*, *A. lumbricoides* and hookworm.	The programme did not have a large effect on the prevalence of *T. trichiura* infections, which remained at 85-97% in all three groups. However, it did reduce the intensity. Twice yearly deworming reduced the prevalence of moderate to severe anaemia by 47% and thrice yearly reduced the prevalence by 57%.	Stoltzfus *et al*, 1998

Table 2 : Summary of studies and trials done on *Trichuris* (see list of abbreviations on page vii).

Country	Study design and sample size	Descriptive measures or hypothesis	Results, comments and conclusions	Reference
Tanzania	**Randomised controlled trial.** 4 schools each were randomised to control, twice a year deworming with single 500 mg dose of mebendazole, or 3 times a year. Children were infected by *T. trichiura*, *A. lumbricoides* and hookworm.	Baseline and 12 month follow-up data on helminth infection to evaluate 2 school-based anthelmintic chemotherapy regimens.	Intensity of *Trichuris* infection declined by 40.4% when treated twice a year and by 75.9% when treated 3 times a year. These results suggest that school-based programmes can be a cost-effective approach for controlling the intensity of intestinal helminth infection even in environments where transmission is high.	Albonico *et al*, 1999
Guinea	**Randomised controlled trial.** 1 child was selected from each of 286 households from 3 villages. Houses were defined by using a table of random numbers.	Information on the relationship between geophagia and infection with intestinal nematodes acquired by ingestion of earth, such as *Trichuris*, or by skin penetration was collected by questionnaire.	Geophagia is a specific risk factor for infection with orally acquired soil-transmitted nematode parasites such as *Trichuris*, but not for parasites that infect primarily through the skin. Education regarding geophagia prevention should be an integral component of any soil-transmitted parasite control programme.	Glickman *et al*, 1999

Table 2 : Summary of studies and trials done on *Trichuris* (see list of abbreviations on page vii).

Country	Study design and sample size	Descriptive measures or hypothesis	Results, comments and conclusions	Reference
Bangladesh	**Randomised controlled trial and intervention**. 4 discrete geographic areas. 550 children between 2-8 years. Children were infected by *T. trichiura, A. lumbricoides* and hookworm.	Cost effectiveness of 4 different regimens in reducing prevalence and intensity of *Trichuris* over 18 months. 1. Albendazole at baseline only. 2. Albendazole at baseline and again at 6 and 12 months and regular health education throughout the study. 3. Albendazole to all members of the household at the commencement of the study and subsequent chemotherapy to all children at intervals of 6 months. 4. Same as group 3 with the addition regular health education throughout the study period.	Albendazole is a broad spectrum anthelmintic and the cost effectiveness of the four interventions were compared by the weighted percentage reduction in prevalence and intensities as measured by geometric mean egg load. Single albendazole mass chemotherapy at an interval of 18 months was the most cost-effective. Egg counts were reduced by 99%. This results suggest that community-based mass chemotherapy per se on a regular basis will meet short-term objectives and is the most cost effective. Long term objectives should look carefully into the possibility of incorporating simple health messages into common health delivery strategy that does not require a separate and costly health education component.	Mascie-Taylor *et al*, 1999

Table 2 : Summary of studies and trials done on *Trichuris* (see list of abbreviations on page vii).

Country	Study design and sample size	Descriptive measures or hypothesis	Results, comments and conclusions	Reference
		CASE CONTROLLED STUDIES		
Malaysia	**Case control study**. 67 children with heavy *Trichuris* infection and 73 children with light infection were selected as controls.	Treatment effect (stilbazian iodide or hexylresorcinal enemas, or a combination of both) on nutrition and *Trichuris* status.	Heavy infestation with *T. trichiura* is associated with marked malnutrition. Results also indicated a much higher rate of bacterial and protozoal co-infection in children with heavy infestation. However, the adverse nutritional effects and the symptoms associated with heavy *T. trichiura* infection were reversible with appropriate diagnosis and specific anthelmintic treatment.	Gilman *et al*, 1983
West Indies	**Case controlled study**. 28 children with *Trichuris* dysentery syndrome were compared with 16 control children (with no TDS or visible worms on colonoscopy).	Rectal biopsy samples were taken before and after expulsion of the worms by means of mebendazole treatment.	Children with TDS had significantly greater numbers than controls of mast cells and of cells with surface IgE in the subepithelial region of the mucosa. Rectal biopsy samples from parasitised children showed high rates of spontaneous histamine release, but only low rates of antigen-specific release. After treatment, spontaneous histamine release was significantly reduced and antigen-specific histamine release could be provoked, showing that immunological memory was established.	Cooper *et al*, 1991

Table 2 : Summary of studies and trials done on *Trichuris* (see list of abbreviations on page vii).

Country	Study design and sample size	Descriptive measures or hypothesis	Results, comments and conclusions	Reference
West Indies	**Case controlled study**. 19 children with TDS and 19 controls.	Relationship between *Trichuris* infection and mental development and growth.	Locomotor development and growth of children with TDS improved significantly after deworming and without nutritional supplementation. Mental development and nutritional status of children with TDS can be considerably impaired. The findings imply that TDS is responsible for at least some of their poor locomotor development.	Callender *et al*, 1992
West Indies	**Case controlled study.** 409 children infected with *T. trichiura* (> 1200 epg) and 205 uninfected children. The children were also infected with *A. lumbricoides*.	Epg, school achievement, attendance and nutritional status.	After controlling for socioeconomic status, gender, age, school and the presence of *Ascaris* infections, the uninfected children had higher reading and arithmetic scores than children with infections of more than 4000 epg and were taller than those with intensities greater than 2000 epg. There were no significant differences in spelling, school attendance and body mass index. These results indicate that moderate levels of infection are associated with poor school achievement and growth.	Simeon *et al*, 1994
West Indies	**Case controlled study**. 409 children infected with *Trichuris* and *Ascaris* and 207 uninfected controls.	Haemoglobin and red blood cell parameters. Hb - Haemoglobin. MCV - Mean corpuscular volume. MCH - Mean corpuscular haemoglobin. MCHC - Mean corpuscular haemoglobin concentration.	Compared to the rest of the children, those with heavy infections (>10 000) had significantly lower ($P<0.5$) Hb, MCV, MCH and MCHC. The prevalence of anaemia (Hb<11.0 g/dl) amongst heavily infected children (33%) was significantly higher ($P<0.05$) than the rest of the sample (11%). Iron deficiency anaemia is associated with *Trichuris* infections >10 000 epg, but not with less intense infections.	Ramdath *et al*, 1995

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Country	Study design and sample size	Descriptive measures or hypothesis	Results, comments and conclusions	Reference
Malaysia	**Case controlled study**. Intestinal permeability of 246 early primary schoolchildren at two schools was assessed by using the lactulose/mannitol differential absorption test.	The ratio of the urinary recoveries of lactulose and mannitol was determined after oral administration of a standard solution of the two sugars. Assessment of intestinal permeability was repeated on 100 infected children after treatment and on a cohort of 68 uninfected children. *T. trichiura* and *A. lumbricoides* were the predominant infections.	Helminthiasis exerted only a marginal effect on intestinal permeability.	Mahendra Raj *et al*, 1996
West Indies	**Case controlled study.** Follow-up of 18 cases of TDS compared to matched controls.	Growth and mental development 4 years after treatment for TDS.	Impaired growth and anaemia were eliminated but mental deficiency persisted. The findings indicate that the treatment of children with TDS should include attention to the psychosocial environment as well as providing medical and nutritional care.	Callender *et al*, 1998
		CLINICAL TRIALS		
Malaysia	**Clinical trial** of single doses of 100 mg, 200 mg, 400 mg and 600 mg of mebendazole. 100 mg : low epg 200 mg : increased epg 400 mg: increased epg 600 mg : maximum epg 129 children with very light to heavy infections.	CR and ERR.	100 mg; CR = 61.9%, ERR = 83% 200 mg; CR = 36.1%; ERR = 82.9% 400 mg; CR = 14.3%; ERR = 86.1% 600 mg, CR = 7.1%; ERR = 89% CR obtained with single doses of mebendazole decreased in the heavier infections despite the use of larger doses of the drug. ERR did not decrease.	Kan, 1983a

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Country	Study design and sample size	Descriptive measures or hypothesis	Results, comments and conclusions	Reference
Malaysia	**Clinical trial** with single or multiple doses of oxantel, pyrantel, mebendazole, flubendazole and albendazole alone or combined. 910 children.	ERR and CR, relative to baseline .	Results showed that all anthelmintics, in single or multiple doses, alone or combined with other anthelmintics, effectively reduced *Trichuris* egg output by 80-90%, regardless of degree of infection. Very low single doses of anthelmintics when used alone, effected 57.5% to 68% CR, but only in light infections (<1000 epg). In heavier infections, CR was 7,1% to 47,6%.	Kan, 1983b
Malaysia	**Clinical trial** using single albendazole doses of 400 mg, 600 mg and 800 mg in 91 patients with single (*Trichuris*) or mixed infections (*Trichuris, Ascaris* and hookworm).	ERR and CR 21 days post-treatment.	400 mg; CR = 27.3%; ERR = 39.2% 600 mg; CR = 60.9%; ERR = 85.1% 800 mg; CR = 48%; ERR = 72.8% Recommended dosage for *Trichuris* is 600 mg single dose.	Ramalingam *et al*, 1983
Malaysia	**Clinical trial** using mebendazole + levamisole as follows : 100 mg + 50 mg; 200 mg + 50 mg; 400 mg + 50 mg; 600 mg + 50 mg and single doses of 100, 200, 400 and 600 mg mebendazole.	ERR and CR relative to baseline.	ERR for combinations of mebendazole and levamisole were 82.6% - 94.5 % compared to 83% - 89% of the mebendazole alone. CR was 31.6% - 55.6% for dual therapy compared to 7.1% - 61.9% for mebendazole. Dual therapy had no advantage. Children were infected with *Trichuris* and *Ascaris*.	Kan & Chua, 1985

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Country	Study design and sample size	Descriptive measures or hypothesis	Results, comments and conclusions	Reference
Malaysia	**Clinical trial**. 57 children infected by *T. trichiura* and *A. lumbricoides*.	Efficacy of single 400 mg dose of albendazole in terms of CR and ERR .	Light infections (<2000 epg); CR = 51,4%; ERR = 57,2% Moderate infections (2000-5000 epg); CR = 28,6%; ERR = 79,3% Heavy infections (>5000); CR = 0; ERR = 61.4%. Hypothesise that heavy *Trichuris* infections probably shorten contact time with anthelmintic, because they cause intestinal hurry.	Ow-Yang & Hanjeet, 1986
Taiwan	**Clinical trial**. 111 children received 200 mg albendazole and 63 received 400 mg.	Cure rate (CR) and egg reduction rate (ERR). Children were infected by *T. trichiura*.	60 days after treatment relative to baseline 200mg; CR = 41.4%, ERR = 85% 400mg; CR = 23.8%, ERR = 59.5% No explanation is given why the higher dose gave worse results.	Chen *et al*, 1990
Sri Lanka	**Clinical trial**. 443 children from a low income group and 224 children from low and lower-middle income groups. Treatment with either single dosages of 400 mg albendazole, 40 mg levamisole, 200 mg mebendazole, 500 mg mebendazole or 250 mg pyrantel pamoate.	CR and ERR relative to baseline. Children were infected by *T. trichiura, A. lumbricoides* and *Necator americanus*.	400mg albendazole; CR = 37.5%, ERR = 87.2% Levamisole; CR = 18.8%, ERR = 72.9% 200 mg mebendazole; CR = 37%; ERR = 73.3% 500 mg mebendazole; CR = 36.2%; ERR = 79.5% Pyrantel pamoate; CR = 22.6%; ERR = 53.8%	Ismail *et al*, 1990

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Thailand	**Clinical trial**. 112 children receiving single 400 mg dose of albendazole; 12 received a 400 mg single dose for 2 consecutive days; 12 received single 400 mg dose for 3 consecutive days; 11 received 2 tablets of placebo on the same day.	CR and ERR on day 7, 14 and 21. Children were infected by *T. trichiura*.	400 mg; CR =4.2%, 7.1%, 77.7%; ERR = 99.2%, 99.6%, 99.5%. 800 mg; CR = 75%, 91%, 94.4%; ERR = 94.4%, 99.8%, 99.8%. 1200 mg; CR = 83.3%, 91.6%, 100%; ERR = 99.4%, 99.8%, 100%. Placebo; CR = 0%, 0%, 9%; ERR = 14.4%; 10.5%, 1.2%.	Setasuban *et al*, 1990
Bangladesh	**Clinical trial**. 245 children infected with *Trichuris*, 143 of whom were also infected with *A. lumbricoides*, treated with albendazole as follows : single doses of either 600 mg or 800 mg or daily doses of 400 mg for either 3 or 5 days.	CR and ERR.	Single doses gave poor ERR and CR of less than 30% each, and 400 mg albendazole for 3 days was required to achieve a CR of 80%. *Trichuris* is relatively refractory. CR for *A. lumbricoides* were 100% for all doses.	Hall & Nahar, 1994
		REVIEWS		
Carribbean (West Indies)	**Review** of health significance of human *Trichuris*.	Prevalence and population dynamics.	*Trichuris* is one of the most prevalent of geohelminths in man. Prevalence and morbidity is grossly underestimated. ***Trichuris* is intrinsically more resistant to control**.	Bundy, 1986
International	**Review** of clinical epidemiology of trichuriasis.	Prevalence, clinical signs, growth, epidemiology and pathology.	Trichuriasis can be clinically serious.	Cooper & Bundy, 1988
International	**Review** of immunological response to *Trichuris* in mice.	Mechanisms of immunity operating during acute versus chronic infection.	Th2 type response is important in resistance to intestinal nematode parasites.	Else & Grencis, 1991

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Country	Study design and sample size	Descriptive measures or hypothesis	Results, comments and conclusions	Reference
International	**Review** of helminth epidemiology including *Trichuris*.	Age related prevalence and intensity.	Definition of methods to evaluate control and prevention.	Bundy *et al*, 1992
International	**Review** of helminths and nutrition, including *Trichuris*.	Significance of helminths, including *Trichuris* in nutrition.	Treatment of infections on a wide scale in most developing countries could decrease malnutrition and improve overall health and well-being of people.	Stephenson, 1994
International	**Review** of chemotherapy of helminths, including *Trichuris*.	*Trichuris* is relatively refractory to anthelmintics, but reductions in prevalence and intensity can be achieved.	Control of helminths should be part of holistic health care programmes.	WHO, 1996
International	**Review.** Tropical medicine : achievements and prospects.	Overview of helminth epidemiology including that of *Trichuris*, the impact on health and new advances in treatment and community control.	Numerous international and national NGO's are including deworming in their health promotion strategies. School based delivery is an important approach to anthelmintic distribution.	Bundy & de Silva, 1998
International	**Review.** Reducing intestinal nematode infection : efficacy of albendazole and mebendazole	Analysis of published data on CR and ERR in the treatment of *T. trichiura* to discuss whether benchmark parasitological drug efficacy rates can be defined for these anthelmintics.	Single-dose albendazole and mebendazole show poor levels of drug efficacy against *Trichuris*, particularly in terms of CR. The median CR for a single dose of 400 mg albendazole is only 38%, with individual studies reporting CR's ranging from 4.9% to 99.3%.	Bennet & Guyatt, 2000
International	**Review.** Do intestinal nematodes affect productivity in adulthood.	Analysis of indirect evidence of several studies suggesting an effect on adult productivity.	Infections can lead to anaemia and wasting, which have been associated with reduced physical fitness, wage earning capacity and productivity. The contemporaneous effects of ill-health in children have potential longer-term consequences for productivity in adulthood.	Guyatt, 2000

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Country	Study design and sample size	Descriptive measures or hypothesis	Results, comments and conclusions	Reference
		CROSS-SECTIONAL STUDIES		
West Indies	**Cross-sectional study**. Helminth infection from age-stratified sample of 244 children of the population was assessed using anthelmintic expulsion techniques after treatment with 100mg mebendazole twice daily for 3 days.	Counting the worms expelled after treatment provides an estimate of infection intensity which is within 90% of the true worm burden.	*T. trichiura* has a higher transmission rate than *A. lumbricoides* even under the same environmental conditions. ***Trichuris* more resistant to control**.	Bundy *et al*, 1987
Malaysia	**Cross-sectional study**. 2938 children.	Prevalence and distribution of trichuriasis in a population of school children living on rural estates and in urban slums, flats and houses within the city.	School children from the rural estates had the highest prevalence (68.4%), followed by those from urban slums (48%). 5.3% of children living in flats or tenement houses within the city had trichuriasis.	Kan, 1987
Brazil	**Cross-sectional study**. 252 children aged between 6 and 60 months.	Association between *Ascaris, Trichuris* and malnutrition.	Higher risk of malnutrition were found in children older than 24 months infected with *Ascaris, Trichuris* or with more than three different parasites.	Sawaya *et al*, 1990
West Indies	**Cross-sectional study**. 593 children.	Association between academic performance and *Trichuris* infection.	67.4% of children were infected with *Trichuris*. Consistent trend for prevalence of *Trichuris* infection to be highest in children judged to be least academically able.	Nokes *et al*, 1991

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Country	Study design and sample size	Descriptive measures or hypothesis	Results, comments and conclusions	Reference
West Indies	**Cross-sectional study**. 51 children.	Rate of exposure to geohelminth infection of children, living in two institutions, was estimated from the product of their rates of ingestion of soil and the density of parasite eggs.	The estimated individual rates of exposure correlated significantly with the observed worm burdens in children at one of the homes, but not at the other. It is suggested that the susceptibility of the children and the distribution of the infective stages in the environment may be important in determining the relationship between exposure and rate of infection.	Wong *et al*, 1991
China	**Cross-sectional survey**. 1.48 million people distributed in 2848 sites from 726 counties in China.	The number of infections due to *Trichuris* in China was estimated at 212 million. Higher prevalences of trichuriasis were found in the age group of 5-9, 10-14 and 15-19 years.	Prevalence of helminthiasis was found to be closely associated with climatic and geographical factors. In view of the morbidity and mortality due to these helminthiasis, their control, particularly in school children, is very important.	Long-Qi *et al*, 1995
Tanzania	**Cross-sectional study**. 203 children.	Relationship among helminths, intestinal blood loss and iron status. Infection intensity was quantified by faecal egg counts, iron deficiency was defined by low haemoglobin and serum ferritin concentrations. Intestinal blood loss was quantified by measuring faecal heme and heme breakdown products.	*T. trichiura* infections was positively associated with faecal Hb, when occurring with hookworm. It is possible that *Trichuris* associated blood loss would be measurable in populations in which hookworm is not present.	Stoltzfus *et al*, 1996
West Indies	**Cross-sectional study**. 800 children.	Relationship of nutritional status, anaemia and geohelminth infections to school achievement and attendance.	Children with *Trichuris* infections had lower achievement levels than uninfected children in spelling, reading and arithmetic.	Hutchinson *et al*, 1997

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Country	Study design and sample size	Descriptive measures or hypothesis	Results, comments and conclusions	Reference
Malaysia	**Cross-sectional study**. 249 early primary schoolchildren.	Effect of intestinal helminths, including *Trichuris* on school attendance.	203 children were infected with *T. trichiura*. Infected children were treated with 400 mg albendazole. Absenteeism rate did not improve more among infected children after treatment compared to the uninfected children.	Mahendra Raj *et al*, 1997
Tanzania	**Cross-sectional study**. Analysis of associations among *T. trichiura*, *A. lumbricoides* and hookworm.	In order to estimate the potential benefits of interventions against multiple geohelminth species (including *T. trichiura*) in endemic areas, an improved understanding of the population biology of multiple infections is required.	Individuals with multiple species infections are likely to be at highest risk of geohelminth-related morbidity, not only because of the number of infections they harbour, but also because they generally carry heavier infections of each species.	Booth *et al*, 1998
Kenya	**Cross-sectional survey**. 204 children.	Geophagy and helminth infections.	Geophagy is a likely source of trichuriasis among primary school children.	Geissler *et al*, 1998
Nicaragua	**Cross-sectional survey**. 961 children.	Correlation between malnutrition, helminthiasis, including *Trichuris*, and child development.	*Trichuris* was more prevalent in malnourished children. Trichuriasis seems to impair development.	Oberhelman *et al*, 1998
Malaysia	**Cross-sectional study**. 104 children.	Trichuriasis may cause intestinal bleeding in the absence of the dysentery syndrome.	But no occult blood was detected in stools by means of a commercially available guaiac test.	Mahendra Raj, 1999
		CASE REPORTS		
Panama	**Case report** of severe trichuriasis. 4 children.	Unique description of clinical progression and gross pathology at necropsy.	Extreme emaciation . Rectal prolapse. No. of worms per case was 1100, 1700, 4100 and 400. Complicated trichuriasis can be lethal.	Getz, 1945

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Venezuela	**Case report**. 9 children.	Blood loss due to *Trichuris* infection was determined by erythrocyte tagging. 24 hrs after tagging, stools were collected. Amount of faecal blood loss/day was determined by dividing the total radioactivity in the faeces during each period by the radioactivity found in the blood at the beginning of every collection period.	Blood loss, although less than that produced by hookworm, is able to induce iron deficiency anaemia.	Layrisse *et al*, 1967
India	**Case reports** of 3 children suffering from severe *Trichuris* infestation.	Intestinal structure and function associated with severe *Trichuris* infection.	Chronic watery diarrhoea. Iron deficiency anaemia. After treatment, the clinical picture improved.	Mathan & Baker, 1970
Columbia	**Case report** of 6 children with moderate to severe *Trichuris* infection.	Blood loss.	In absence of dysentery, daily gastro-intestinal blood loss is negligible in healthy children with heavy infections.	Lotero *et al*, 1974
South Africa	**Case report**. 10 children.	Clubbing, growth retardation, pallor, abdominal distension , bloody diarrhoea and *Trichuris* infestation	Weight gain after treatment. Clubbing reversed after 3 months. Eosinophilia present in 8 of the children.	Bowie *et al*, 1978
South Africa	**Case report** of a 45 year old woman with massive *Trichuris* infection.	Description of *Trichuris* infection in the colon and rectum stimulating Chrohn's colitis.	Persistent diarrhoea, abdominal pain, loss of weight. After treatment with mebendazole for 2 weeks symptoms disappeared.	Sandler, 1981
West Indies	**Case study** of 9 children with intense symptomatic *Trichuris* infection.	Growth velocities following expulsion of *Trichuris* by mebendazole (100 mg 2x daily for 3 days).	Accelerated growth on recovery from TDS.	Cooper *et al*, 1990

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Country	Study design and sample size	Descriptive measures or hypothesis	Results, comments and conclusions	Reference
		FOLLOW-UP STUDIES (PROSPECTIVE STUDIES)		
West Indies	**Prospective study**. 19 infected children. Single 400 mg dose or 2 consecutive doses of albendazole.	Rate of expulsion of worms.	It is necessary to know when worms are expelled after deworming to estimate worm burdens (intensity). Maximum worm expulsion rate was attained on the 4th day regardless of the treatment. Expulsion started 48hrs after deworming.	Bundy *et al*, 1985a
West Indies	**Prospective study**. *Trichuris* infection in 23 children were assessed by stool collection for more than 5 days after treatment with mebendazole.	Population distribution of *Trichuris* based on maximum rate of worm expulsion.	In order to measure worm burden it is necessary to know when worms are expelled after deworming. Maximum rate of worm expulsion was achieved on the 4th day after starting treatment with 100 mg mebendazole. This confirms results with albendazole (Bundy *et al*, 1985a)	Bundy *et al*, 1985b
West Indies	**Prospective study**. Deworming intervention. 2500 children treated with a single dose of albendazole in four sequential cycles at intervals of four months.	Prevalence and intensity of *Trichuris*.	The programme delivered treatment to greater than 90% of the target population in each cycle, and reduced the prevalence and intensity of *Trichuris* infection in the target age-class. This study demonstrates that chemotherapy targeted only at children can be implemented within an existing health infrastructure and can achieve overall reduction in the prevalence and intensity of geohelminth infection.	Bundy *et al*, 1990

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Country	Study design and sample size	Descriptive measures or hypothesis	Results, comments and conclusions	Reference
Mexico	**Prospective study**. 2094 members of 2 communities.	Study of familial dispersion of *Trichuris* infection intensity before and after deworming.	Persons heavily infected with *Trichuris* tend to become heavily reinfected. The mean family eggs per gram/stool were similar before the 1st treatment and after 6 months of reinfection.	Forrester *et al*, 1990
Tanzania	**Follow-up study.** 731 children.	The comparative efficacy of albendazole and mebendazole in the treatment of intestinal nematode infections were compared. The rate of re-infection three weeks, four months and six months after treatment was determined, as well as the appropriate interval between treatments.	Differences in the efficacies were apparent 21 days after treatment, but were no longer apparent four months after treatment. By six months, intensities of infection were similar to pre-treatment level. The treatment of schoolchildren every four months may be necessary in highly endemic areas in order to have an impact on the intensity of intestinal nematode infections, sufficient to be likely to reduce morbidity.	Albonico *et al*, 1995
MATHEMATICAL EPIDEMIOLOGY OF HELMINTHIASIS (INCLUDING TRICHURIASIS)				
International	**Mathematical study.** Essay discussing some pitfalls and possible sources of inaccuracy or error in method of diagnosis and quantification.	Reliability of diagnosis based on microscopy. Quantifying of helminth burdens by estimating the concentration of eggs in a unit quantity of faeces (epg).	Growing body of evidence to indicate that faecal egg counts show variation from day to day. Single sample egg counts may be unreliable. Some doubts must remain about some of the studies which have attempted to determine the daily egg production of worms by estimating egg counts from 24 hour faecal collections and then treating infections in order to recover and count female worms.	Hall, 1982

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Country	Study design and sample size	Descriptive measures or hypothesis	Results, comments and conclusions	Reference
International	**Mathematical study**, review of the population and transmission biology of major helminth infections of man. Acquired immunity and contact with parasites change with age. The degree and frequency of mass chemotherapy influence parasite prevalence and intensity. Effects of selective or targeted chemotherapy and predisposition to heavy infection.	Design of mass and targeted community-based chemotherapy programmes for the control of the major helminth infections in relation to the population and transmission dynamics of the parasites in the human population.	Rapid reinfections following a single mass or targeted anthelmintic application is a universal feature of helminth transmission. Control of reinfection requires repeated community treatment. The degree of application and the interval between treatments are dependant on the reproductive life expectancy of the adult worm, the net force of transmission prior to control and the factors which create aggregation in the distribution of parasite loads within the population. Selective or targeted treatment is shown to be most effective for the control of morbidity in individuals as opposed to the control of transmission.	Anderson & Medley, 1985
International	**Mathematical study.** An attempt to define a method for estimating the global morbidity due to human intestinal nematode infections, including *T. trichiura*, based on the observed prevalence of infection.	The method relies on the observed relationships between prevalence and intensity of infection and between worm burden and potential morbidity.	Present estimates suggest that the potential morbidity attributable to geohelminthiasis is much greater than previously supposed. Morbidity is associated with 8-13% of *T. trichiura* infections. This includes both clinical and developmental effects. Results also conclude that control should be targeted at school-age children. This proposed method provides a possible framework whereby global morbidity may be estimated in the absence of any direct means of measurement.	Chan *et al*, 1994

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South Africa	**Mathematical study**. Changes in prevalence of intestinal nematodes were investigated along an altitudinal transect from approximately 50 m above sea level. 693 primary schoolchildren aged between 7-15 years from six communities were examined along a 150 km transect.	The effects of climate and topography on the distribution of common intestinal nematodes in schoolchildren.	Changes in the prevalence of *T. trichiura* were significantly correlated with temperature derived variables. Marked drop in prevalence of *Trichuris* at altitudes higher than 1000 m.	Appleton & Gouws, 1996
International	**Mathematical study**. A literature search was conducted for surveys which reported the prevalence and frequency of multiple species geohelminth infections in human communities. Data from 24 surveys were analysed.	A probalistic model is used to predict the prevalence of multiple species geohelminth infections.	The model was found to provide a reasonably accurate prediction in most communities. Data from almost half the communities analysed showed evidence of statistical interaction between *A. lumbricoides* and *T. trichiura*. Age-stratified analysis reveals that the degree of interaction between these two infections does not alter significantly with age in the Malaysian children.	Booth & Bundy, 1995

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Country	Study design and sample size	Descriptive measures or hypothesis	Results, comments and conclusions	Reference
International	**Mathematical study**. A review of the use of chemotherapy for the control of morbidity due to soil-transmitted nematodes in humans.	Evaluation of the efficacy of anthelmintics in terms of CR and ERR. CR-proportion of patients treated who are egg negative on one follow-up examination on a single stool sample. ERR-percentage fall in egg counts after anthelmintic chemotherapy based on a follow-up examination of a stool sample.	Albendazole : CR for *T. trichiura* between 10% and 67% and ERR between 73% and 87% in comparative trials with mebendazole. Ivermectin: 11-100% (CR) effective on *T. trichiura* according to the different dosage used (from 200µg/kg single dose to 400 µg/kg in 2 divided doses with administration over 2 days). Levamisole : The drug has a more variable effect against *T. trichiura* (CR = 16-18%, ERR = 73%). Mebendazole : In comparative trials with albendazole, the efficacy of the single dose is similar for *T. trichiura* (CR = 14-70%, ERR 80-89%).	WHO, 1996
Kenya	**Mathematical study**. A community-based epidemiological survey of 752 persons in three villages. 79% of school-aged children were enrolled in the study.	Estimation of : 1) the proportion of infected persons who would be treated, and 2) the effect on helminth egg production, by providing anthelmintic to children at school.	Prevalence of *Trichuris* was 24%. School children had more *Trichuris* infections than peers not attending schools indicating that schools increase transmission of *Trichuris* compared to home environments. Of the total population, school-based programmes would treat only between 31% and 50% of infected persons and eliminate only 29% of *T. trichiura*. It would be efficient in improving helminth status of school-aged children, but adults and preschool children were not offered treatment and they contribute to the helminth egg burden in the area. Mass chemotherapy should therefore be targeted at the community.	Olsen, 1998

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Tanzania	**Mathematical study**. Delivery of anthelmintics to school-aged children through schools compared to treatment based on vertical delivery through the health system, eg. mobile clinics.	Cost of delivery activities that utilise the school system can be nearly an order of magnitude cheaper than the use of a mobile health team.	Delivery of anthelmintics through the schools system as opposed to using a mobile team can reduce delivery costs by an order of magnitude. Due to these low costs, mass treatment for intestinal nematodes may be "good value" even when only 25% of the community are infected.	Guyatt, 1999
Africa	**Mathematical study.** Literature search on age-stratified infection data for intestinal nematode infections. 18 countries and 70 study sites.	Can estimates of prevalence of infection in school-aged children provide an index for determining community prevalence. Observed data on prevalence of infection in infants, school-aged children and adults were fitted using linear and logistic regression models.	The prevalence of infection in school-aged children alone was shown to be higher than the predicted prevalence in the community. A more extensive analysis of *T. trichiura* is needed because data at moderate and high prevalences of infections were limited.	Guyatt *et al*, 1999

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		OPERATIONAL RESEARCH		
International	**Operational research** Theoretical.	Review of what is known about the health of school-age children, what is or can be done to improve health, what steps must be taken to find ways to improve health and educational achievement of children.	1. School-age children of developing countries face health problems that remain neglected and poorly understood. 2. Operational research needed is to develop similar means of monitoring the health status of school-age children and evaluating the impact of public health interventions of this age group. 3. To further develop and test programmes that appear to offer effective means of improving health of this age group at reasonable cost and to develop the capacity within countries to assess health problems and devise cost effective strategies.	Bundy & Guyatt, 1996
International	**Operational research**. Document information that will help implement interventions that will reduce helminth infections through school by relatively low-cost programmes at schools.	Convincing others that helminth reduction by means of interventions in schools is important and that it really works well; planning of interventions; integrating helminth reduction intervention within various components of a school health programme.	Schools provide the most effective and efficient way to reach large proportions of the population, including young people, school personnel, family and community members, and to reduce infections and prevent re-infections. These efforts may be most effective when integrated into more comprehensive approaches to school health, such as development of health promoting schools.	WHO, 1997

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Country	Study design and sample size	Descriptive measures or hypothesis	Results, comments and conclusions	Reference
International	**Operational research**. Management of drug failure and drug resistance, if it should eventually be recognised in community-based interventions.	Definition of drug resistance, development of a standard protocol to monitor and recognise it in control programmes and give guidelines to continue to sustain control activities.	Assessment of drug efficacy is not straightforward, because there are many potential measures of efficacy. It also needs to be distinguished from effectiveness. Efficacy is the effect of a drug against an infective agent in ideal experimental conditions and isolated from any practical context, whereas effectiveness measures end-user acceptance and compliance in the face of practical realities which include side effects and cost.	WHO, 1998a
International	**Operational research**. Diagnosis of helminths, including *T. trichiura* in children at schools, by stool examination. Planning and managing a school survey, analysis of results, implementing treatment and evaluating control measures.	Guidelines for the evaluation of soil-transmitted helminthiasis and schistosomiasis at community level.	The relevant parameters to guide the decision making process for the control of soil-transmitted helminthiasis are prevalence of infections, which gives information on the number of infected people in a population, and intensity of infection, which gives information on the severity of an infection. The first objective of any control program is the reduction of the proportion of highly infected individuals, because this will be accompanied by a reduction in morbidity.	Montresor *et al*, 1998
International	**Operational research**. Monitoring helminth control programmes.	Monitoring the impact of control programmes aimed at reducing morbidity caused by soil-transmitted helminths, including *T. trichiura*.	Monitoring is essential in ensuring that programmes are run effectively and efficiently by health and school authorities and that maximal benefit is attained by infected individuals, their families and communities.	Montresor *et al*, 1999

Analysis of the spread of literature on *Trichuris* internationally is presented in Table 3, and by study design in Table 4.

Table 3 : Distribution of literature on *Trichuris* by countries or continents.

Country/Continent	Number of papers	Percentage of total
International	18	21.9
West Indies	16	19.5
Malaysia	10	12.2
Tanzania	7	8.5
South Africa	5	6.0
Kenya	5	6.0
Thailand	4	4.8
Indonesia	2	2.4
Mexico	2	2.4
Bangladesh	2	2.4
Africa	1	2.4
Brazil	1	1.2
Columbia	1	1.2
Guatemala	1	1.2
Guinea	1	1.2
India	1	1.2
Nicaragua	1	1.2
Panama	1	1.2
Sri Lanka	1	1.2
Taiwan	1	1.2
China	1	1.2
Venezuela	1	1.2
TOTAL	**83**	

Table 4 : Distribution of literature on *Trichuris* by study design.

Study design	Number of papers	Percentage of total
Randomised placebo controlled trials and intervention surveys.	19	22.9
Case controlled studies.	7	8.5
Clinical trials.	9	11.0
Reviews	9	11.0
Cross-sectional studies	13	15.9
Case reports	7	8.5
Follow-up studies (Prospective studies)	5	6.1
Mathematical epidemiology of helminthiasis	9	11.0
Operational research	5	6.1
TOTAL	83	

Both the international and national literature on *Trichuris* appears to be impoverished, as there are only 77 papers since 1980 dealing with this helminth. Prior to this period, most of the papers on *Trichuris* were case reports (Getz, 1945; Layrisse *et al*, 1967; Lotero *et al*, 1974; Mathan & Baker, 1970; Bowie *et al*, 1978). The proportion of studies with research power, in the form of randomised controlled trials, case control studies and clinical trials, are 42.4% or 35 publications. Of these papers, 16 conclude that trichuriasis is associated with significant clinical (5 papers) and subclinical (11 papers) effects. The rest report on the efficacy of the different anthelmintics on *Trichuris*. The clinical effects described included stunting, wasting, rectal prolapse, finger clubbing, diarrhoea, anaemia, dysentery, appendicitis and colitis. The subclinical effects were impairment of mental development, cognitive function, co-ordination, motor function, learning, school attendance, nutrition and weight-for-age. In South Africa there is a need for more studies, especially because of the possible link between the immunological response to trichuriasis and other helminthiasis, and increased susceptibility to HIV and tuberculosis (Bentwich *et al*, 1999; Fincham *et al*, 1999; Markus & Fincham, 2000). In common with many other developing countries, epidemics of HIV/AIDS and Tuberculosis are out of control. Programming of the immune system by *Trichuris*, and other helminthic infections (Bentwich *et al*, 1996; Bentwich *et al*, 1997; Adams *et al*, 1999; Fincham & Markus, 1999; Fincham *et al*, 1999; Markus & Fincham, 2000) may also enhance progression to AIDS and activation of tuberculosis, and is likely to impair efficacy of vaccines (Bentwich *et al*, 1999).

Literature specific to efficacy of anthelmintic drugs

There is general consensus that intestinal nematodes cause a significant amount of morbidity in children, and that it can be reduced by the correct use of anthelmintics, as well as by education, proper sanitation and clean water and food. Several drugs have been developed and evaluated for efficacy by the research-based pharmaceutical industry for the treatment and control of nematode infections (WHO, 1996; Montresor *et al*, 1999). Efficacy is defined as the effects of a drug against an infective agent in ideal experimental conditions and isolated from the necessity of voluntary compliance. A review of the literature specific to drug trials (Tables 5 & 6) shows wide variation in reported cure rates achieved. Assessment of drug efficacy is not straightforward, because there are many potential measures of efficacy and, even where similar methods of measurements are used, different drug trials often give divergent results (Montresor *et al*, 1999). Efficacious medications become effective if they are widely used in medical practices and health services and by the public voluntarily. Some highly efficacious chemotherapy is only used in emergencies which threaten life, because normally it is too toxic, carcinogenic or mutagenic or has other unacceptable side effects. Thus the public are not likely to use medication which causes severe nausea or headaches. An example of an ineffective anthelmintic is piperazine, which has been withdrawn from the essential drug list of WHO because the spectrum is too narrow and it is relatively toxic. Poor drug quality will impair efficacy, such as the polymorphs A and B of mebendazole, which are inferior anthelmintics to polymorph C (Charoenlarp *et al*, 1993; Evans *et* *al*, 1999). Ecological, immunological, epidemiological and psychological factors contribute to efficacy and effectiveness. Moreover there are several other factors which can influence assessment of efficacy and effectiveness. These include rapid transit through the intestine due to diarrhoea and dysentery, intensity of infection, variability in the rate of egg laying and excretion, frequent transmission of infection, examination of stools too soon after treatment, lack of compliance by patients, untrained health workers, poor quality diagnostic procedures and drug resistance. Resistance has developed to some anthelmintics which were efficacious against schistosomes, such as oxamniquine (WHO, 1998b; Montresor *et al*, 1999). It must be also be recognised that the pharmaceutical performance of apparently identical products (generics) may be variable (Charoenlarp *et al*, 1993; WHO, 1996; WHO, 1998b; Evans *et* al, 1999).

Note that the meanings of cure rate (CR) and egg reduction rate (ERR), which are used in Tables 5 and 6, are defined in the list of definitions at the beginning of this thesis. Numbers in superscript in Table 5 refer to footnotes.

Table 5 : Anthelmintic efficacy against *Trichuris trichiura* in terms of cure rate (CR) and egg reduction rate (ERR) in stools.

Anthelmintic	Dosage	CR (%)	ERR (%)	Total patients	*Mean epg before treatment	Reference
oxantel pyrantel	10 mg/kg (single)	68.0%	90.0%	50	375	Kan 1983a[1]
oxantel pyrantel	15 mg/kg (single)	62.3%	92.0%	61	705	
oxantel pyrantel	20 mg/kg (on three successive days)	66.7%	94.5%	24	2 833	
oxantel pyrantel + mebendazole	10 mg/kg+100mg (single)	78.3%	89.3%	106	14 822	
oxantel pyrantel + mebendazole	15 mg/kg+100 mg (single)	84.3%	90.0%	48	3 003	
oxantel pyrantel + mebendazole	15 mg/kg+200 mg (single)	75.9%	93.8%	29	7 426	
mebendazole	100 mg (twice daily for three days)	52.0%	91.2%	25	6 472	
mebendazole+levamisole	100 mg+50 mg (single)	50.0%	86.6%	18	506	
flubendazole	200 mg (single)	47.6%	92.4%	42	1 638	
flubendazole	500 mg (single)	17.3%	93.1%	52	11 241	
flubendazole	600 mg (single)	18.8%	91.2%	32	7 816	
flubendazole	300 mg (repeated the next day)	65.1%	94.5%	43	6 669	
flubendazole+ levamisole	200 mg+500 mg (single)	64.7%	94.8%	34	892	
flubendazole+levamisole	500 mg+50 mg (single)	34.2%	88.6%	87	2 896	
albendazole	200 mg (single)	44.8%	91.8%	30	701	
albendazole	600 mg (single)	20.0%	88.8%	60	2 454	

Table 5 : Anthelmintic efficacy against *Trichuris trichiura* in terms of cure rate (CR) and egg reduction rate (ERR) in stools.

Anthelmintic	Dosage	CR (%)	ERR (%)	Total patients	*Mean epg before treatment	Reference
albendazole	400 mg (single)	33.3%	87.8%	33	750	
albendazole	400 mg (single)	31.2%	39.2%	22	273	Ramalingam *et al*, 1983 [2]
albendazole	600 mg (single)	57.1%	85.1%	25	1 694	
albendazole	800 mg (single)	42.3%	72.8%	28	508	
mebendazole	100 mg (single)	61.9%	83.0%	21	601	Kan, 1983b [3]
mebendazole	200 mg (single)	36.1%	82.9%	47	2 233	
mebendazole	400 mg (single)	14.3%	86.1%	21	6 974	
mebendazole	600 mg (single)	7.1%	89.0%	14	22 499	
albendazole	400 mg (single)	68.9%	89.2%	132	<2 000	Rossignol & Maisonneuve, 1983 [4]
albendazole	400 mg (single)	37.5%	87.0%	8	2 000-5 000	
albendazole	400 mg (single)	40.0%	95.0%	5	>5 000	
mebendazole+levamisole	100 mg+50 mg (single)	88.9%	99.8%	36	257	Kan & Chua, 1985 [5]
mebendazole+levamisole	200 mg+50 mg (single)	91.1%	99.5%	57	444	
mebendazole+levamisole	400 mg+50 mg (single)	96.7%	99.6%	39	1 855	
mebendazole+levamisole	600 mg+50 mg (single)	94.1%	99.1%	19	3 513	
mebendazole	100 mg (single)	100%	100%	21	601	
mebendazole	200 mg (single)	100%	100%	47	2 233	

Table 5 : Anthelmintic efficacy against *Trichuris trichiura* in terms of cure rate (CR) and egg reduction rate (ERR) in stools.

Anthelmintic	Dosage	CR (%)	ERR (%)	Total patients	*Mean epg before treatment	Reference
albendazole	400 mg (single)	88.8%	83.3%	9	<2 000	Misra *et al*,1985 [6]
albendazole	400 mg (single)	50.0%	70.9%	2	2 000-10 000	
albendazole	400 mg (single)	100%	100%	1	> 10 000	
albendazole	400 mg (single)	51.4%	57.2%	37	<2 000	Ow-Yang & Hanjeet, 1986
albendazole	400 mg (single)	28.6%	79.3%	7	2 000-5 000	
albendazole	400 mg (single)	0%	61.4%	4	>5 000	
albendazole	400 mg (single)	90.5%	-	480	-	Jagota, 1986
mebendazole	500 mg (single)	100.0%	-	7	8-150	Evans, 1987 [7]
albendazole	400 mg (single)	-	28.0%	78	2 857	Stephenson *et al*, 1989 [8]
albendazole	200 mg (single)	17.1%	70.5%	111	339	Chen *et al*, 1990 [9]
albendazole	400 mg (single)	12.7%	61.8%	63	306	
mebendazole	100 mg (repeated after three hours, for three days)	91.0%	98.0%	45	653	
mebendazole	100 mg (repeated after six hours for three days)	93.9%	99.8%	33	540	
mebendazole	100 mg (repeated after 12 hours for three days)	93.8%	98.6%	16	1 593	
oxantel	10 mg/kg	69.0%	87.2%	42	1 362	

Table 5 : Anthelmintic efficacy against *Trichuris trichiura* in terms of cure rate (CR) and egg reduction rate (ERR) in stools.

Anthelmintic	Dosage	CR (%)	ERR (%)	Total patients	*Mean epg before treatment	Reference
oxantel	15 mg/kg	76.0%	89.6%	46	1 050	
oxantel	30 mg/kg	84.0%	96.5%	19	1 063	
albendazole	400 mg (single)	31.8%	87.2%	85	2 562	Ismail *et al*, 1990 [10]
levamisole	2.5 mg/kg (single)	18.0%	72.9%	89	1 634	
mebendazole	200 mg (single)	37.0%	73.3%	73	1 121	
mebendazole	500 mg (single)	36.2%	79.5%	94	2 058	
pyrantel pamoate	10 mg/kg (single)	22.6%	53.8%	84	1 416	
albendazole	400 mg (single)	77.7%	99.5%	112	4 310	Setasuban *et al*, 1990 [11]
albendazole	400 mg (repeated next day)	91.6%	99.8%	12	3 228	
albendazole	400 mg (repeated for three days)	100%	100%	12	2 336	
albendazole	400 mg (single)	44.0%	-	48	-	Hanjeet & Mathias, 1991
albendazole	600 mg (single)	67.0%	-	43	-	
ivermectin	150 µg/kg (single)	No significant effect		397	-	Whitworth *et al*, 1991 [12]
albendazole	400 mg (daily for three days)	68.2%	-	54	-	Anantaphruti *et al*, 1992 [13]
mebendazole	100 mg (twice a day for three days)	71.4%	-	64	-	
albendazole	400 mg (single)	33.3%	45.7%	-	-	Bartoloni *et al*, 1993 [14]
mebendazole	400 mg (single)	60.0%	15.0%	-	-	

Table 5 : Anthelmintic efficacy against *Trichuris trichiura* in terms of cure rate (CR) and egg reduction rate (ERR) in stools.

Anthelmintic	Dosage	CR (%)	ERR (%)	Total patients	*Mean epg before treatment	Reference
mebendazole (generic)	300 mg (single)	0%	28.3%	49	-	Jonsuksuntigul *et al*, 1993[15]
mebendazole (original)	300 mg (single)	43.3%	77.9%	49	-	
mebendazole (original)	500 mg (single)	70.3%	89.9%	49	-	
albendazole (original)	400 mg (single)	67.4%	87.0%	49	-	
albendazole	600 mg & 800 mg (single)	<30.0%	<30.0%	245	-	Hall & Nahar, 1994[16]
ivermectin	200 µg/kg	11.3%	59.0%	152	443	Marti *et al*, 1996[17]
albendazole	400 mg (daily for three days)	43.0%	92.0%	149		

* Arithmetic mean

1. Stools were examined before treatment and again 4 weeks after treatment. Mebendazole was combined with oxantel pyrantel in various dosages to reduce the risk of erratic migration of *Ascaris* in mixed infections. All anthelmintics in single or multiple doses, alone or combined with other anthelmintics, effectively reduced *Trichuris* egg output by 80-90%, regardless of the degree of infection. Very low single doses of anthelmintics, when used alone, effected 57.5-68% CR, but only in very light *Trichuris* (<1 000 epg).
2. Post-treatment stool examination done 14 days after treatment. Follow-up survey done 5-6 months afer treatment in 10 of the original cases showed significant reduction in eosinophils at both 600 mg and 800 mg doses.
3. CR varied in proportion to epg. ERR > 80% for all doses and all intensities.
4. Stool examination performed before treatment and 7 and 21 days after treatment. 446 patients received the active drug or the placebo twice daily, while the remaining 424 received a single dose.
5. Post-treatment stools examined 4-6 weeks after treatment.
6. Stool examination repeated on the 14th and 21st day after treatment.

7. Two pre-treatment egg counts and 1 post-treatment count 14 days after treatment.
8. Re-examined 6 months after treatment. Significant weight gain compared to placebo group.
9. Evaluation by 3 consecutive days of stool examination made 3 weeks after treatment.
10. Post-treatment stool examination was carried out 14-21 days after treatment. Higher CR were obtained in lighter *Trichuris* infections.
11. Stool examination done in duplicate of pre-treatment and days 7, 14 and 21 post-treatment. CR and ERR measured on 21 days post-treatment.
12. Stool examination 45-105 days post-treatment.
13. Stool samples obtained 3 weeks after treatment. In high intensity infections, albendazole yielded lower CR than mebendazole. Similar CR obtained in light infections.
14. Albendazole produced a higher ERR, but lower CR compared to mebendazole.
15. Pre-treatment stool examination and post-treatment examination 14 days after treatment.
16. 400 mg on three successive days was required to achieve a CR of 80%. Stools examined over a period of 10 days after treatment and again after 40 days.
17. Follow-up stool examination 3 weeks after treatment. CR low for both drugs.

Table 6. Anthelmintic efficacy against *Trichuris trichiura* in terms of reduction of prevalence (%) and intensity of infection (epg %)

Anthelmintic	Dosage	Prevalence (% reduction)	Intensity (% reduction)	No. of patients	*Epg before treatment	Reference
albendazole	400 mg (single)	78.0%	-	9	2 668	Bundy *et al*, 1985b [1]
albendazole	800 mg (400 mg repeated next day)	78.0%	-	9		
mebendazole	100 mg (x2 daily for three days)	82.6%	99.9%	23		Bundy *et al*, 1985a [2]
albendazole	1200 mg (repeated three times at four month intervals)	93.0%	99.0%	174	1 206	Forrester *et al*, 1998 [3]
albendazole	400 mg (repeated three times at four month intervals)	51.0%	87.0%	160	1 517	
pyrantel	11 mg/kg (repeated three times at four month intervals)	16.0%	67.0%	174	1 506	
albendazole	400 mg (single)	98.0%	47.0%	86	2 383	Hadju *et al*, 1998 [4]
mebendazole	500 mg (single)	85.0%	72.2%	42	899	Jackson *et al*, 1998 [5]
albendazole	400 mg (single)	75.0%	44.0%	40	1 045	

*Arithmetic mean

1. The temporal patterns of expulsion of adult *Trichuris* were similar whether the children received a single 400 mg dose or 2 consecutive doses. The maximum worm expulsion rate was attained on the 4th day.
2. Total 24 hour stool collections were initiated on the first day of therapy and continued for 6 days. Maximum rate of expulsion of adult *Trichuris* occurred on the 4th day.

3. Follow-up 1 year after treatment. 1200 mg albendazole had no effect on growth in height among children with high levels of infections. Better growth in height among children with high levels of infection who received 400 mg. Reduction in prevalence and intensity measured after the final treatment.

4. Re-examined 6 months after treatment. The prevalence of *Trichuris* infections did not change significantly but the intensity of *Trichuris* infections did.

5. Mebendazole was associated with significantly better (P = 0.024) median % reduction in ova count (72.2%) than albendazole (44%).

Conclusions on the literature

1. Only 6% of all detected studies on *Trichuris* emanated from South Africa. This was exceeded by studies in the West Indies (19.5%), Malaysia (12.2%) and Tanzania (8.5%).

2. There is a need for more operational research which analyses performance of programmes which seek to prevent and control helminth infection holistically. The complete approach necessitates effective health education, improvement of hygiene and sanitation, and therapy. Only about 6% of studies were this type of research.

3. Reported efficacy of a range of anthelmintics against *Trichuris*, in terms of CR and ERR, varies widely. There are many possible reasons. It is fundamental that to evaluate efficacy there must be sustained treatment compliance. The confusion that exists emphasises the need to monitor treatment results under local conditions.

CHAPTER 3

The life cycle of *Trichuris trichiura.*

Man is the definitive host and the life cycle is direct, meaning that there are no intermediate hosts. Proof of patent infection is the presence of the distinctive eggs in stools (Fig. 6), because eggs only stem from sexual reproduction by adult worms.

Each female produces from 3 000 to 20 000 eggs per day (Bundy & Cooper, 1989). The appearance and dimensions of eggs are diagnostic. They are barrel-shaped with translucent bipolar plugs which may be mucoid (Connor & Neafie, 1976; Beaver *et al*, 1984). Three layers can be distinguished in the shell by transmission electron microscopy (Appleton & White, 1989). The outer layer is brownish and contrasts can be increased by staining with dilute iodine. The innermost layer is vitteline. Eggs passed in faeces are not embryonated, and therefore not infective.

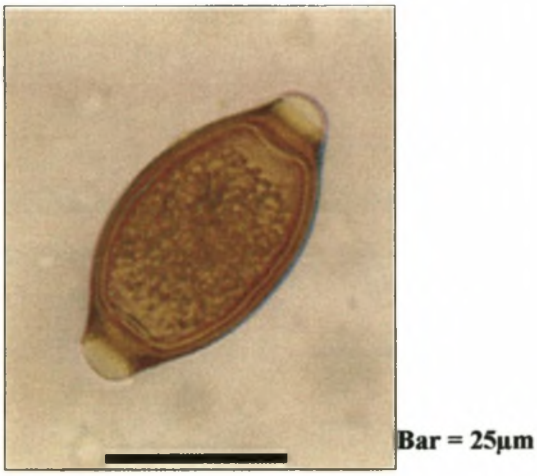

Fig. 6: An embryonated egg of *Trichuris trichiura*. Bar = 25µm. The inner layer of the shell is vitteline and there are bipolar plugs that may be mucoid. Dimensions are 55µm x 22 - 24µm. Reproduced with permission from WHO, 1994.

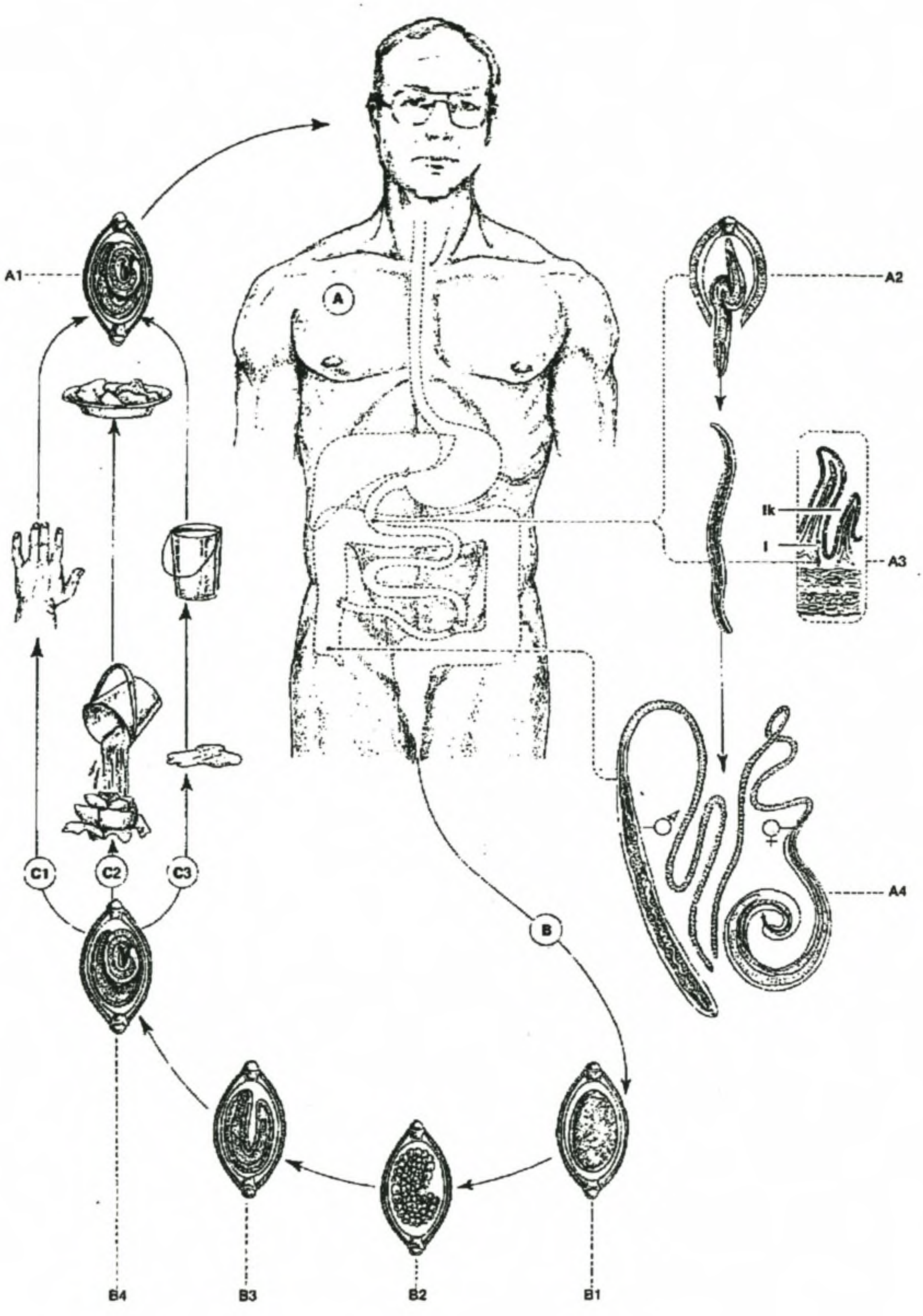

Fig.7: The life cycle of *Trichuris trichiura* (Reproduced from Oberholzer & Ryke, 1993 with permission). See list of alphabetical keys on the following page.

Key to Fig. 7:

A - Development inside the human host.

After faeces containing eggs mix with moist, warm earth, embryonic development proceeds to formation of L1-larvae within eggs (A1). This obligatory period of development within the soil characterises *Trichuris* as a geohelminth or soil-transmitted helminth (WHO, 1996; Montresor *et al*, 1999). Eggs containing viable L1-larvae are infective if swallowed. The juvenile hatches in the small intestine and enters the crypts of Lieberkühn (A2 - A3). After a short period of development, it reenters the intestinal lumen and migrates to the ileocecal area, where it matures in about three months (A4).

B - Development outside the human host.

Under suitable conditions of humidity and warmth, embryonation to L1-larvae is completed in about 21 days (B1 - B4).

C - Transmission.

Faecal - oral transmission is the most common route of infection (C1). Vegetables fertilised with contaminated human faeces is another mode of transmission (C2). Contaminated drinking water is also a possible route (C3).

The epidemiology of trichuriasis.

Trichuriasis is caused by parasitism of the distal intestinal tract of humans by the geohelminth *T. trichiura*. It affects individuals, communities and whole populations of people, mostly causing subclinical morbidity (as defined under key terms).

The distribution of trichuriasis in communities and populations where it is endemic is shown by plotting prevalence in relation to age. In the West Indies, the prevalence of trichuriasis peaks in young school-age children and then plateaus, as depicted in Fig. 8 (Bundy *et al*, 1992).

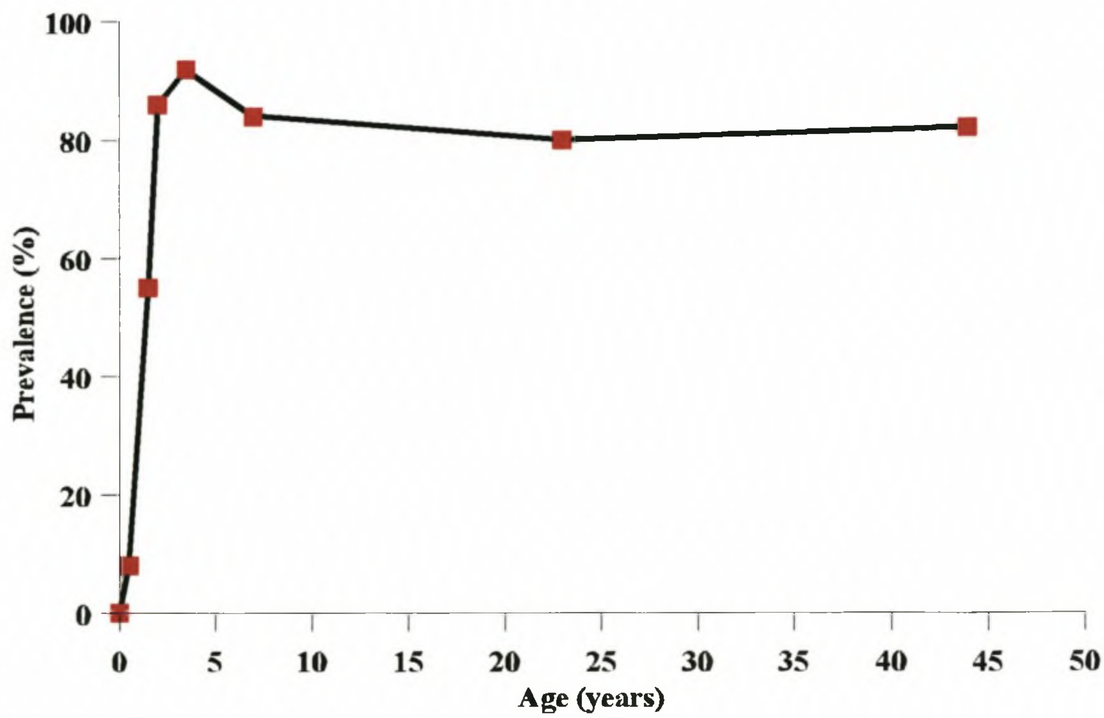

Fig. 8: The typical age/prevalence relationship for infection by *Trichuris trichiura* in the West Indies, according to Bundy *et al*, 1992.

In China higher prevalences of trichuriasis were found in the age groups of five to nine, 10-14 and 15-19 years (Long-Qi *et al*, 1995).

In the West Indies, intensity of trichuriasis, as estimated by egg counts in stools, peaks in primary school children, and then declines with age as shown in Fig. 9 (Bundy *et al*, 1992) in contrast to the way in which prevalence plateaus.

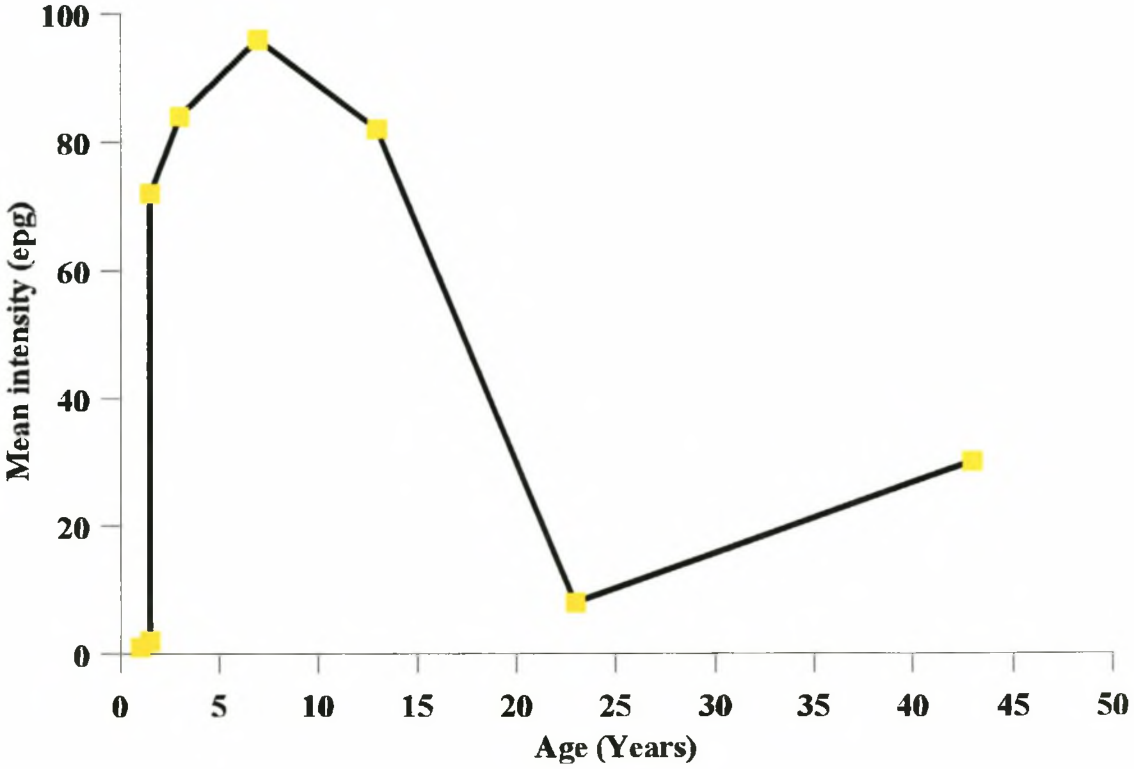

Fig. 9: The typical age/intensity relationship for infection by *Trichuris trichiura* in the West Indies, according to Bundy *et al*, 1992.

Counts of *Trichuris* eggs expressed per gram of homogenised stool reflect the number of adult worms from which eggs originate within the host's intestine (Hall, 1982). For a parasitised individual, it is necessary to count eggs in several stools to obtain a valid mean value. However, the geometric mean or the median count derived in a single cross-sectional study from single stool samples from each child in a large group of children, is a valid estimate for use in analysis of anthelmintic efficacy, or for comparison between communities or populations (Bundy *et al*, 1985b; Anderson, 1986; Bundy *et al*, 1992; Montresor *et al*, 1998).

The pathophysiology of trichuriasis, which is linked directly to the presence of the worms in the caecum, colon and rectum, as described in pathology texts and case reports, is interpreted as primary disease (Getz, 1945; Neafie *et al*, 1976; Beaver *et al*, 1984; Cooper & Bundy, 1988; Cooper *et al*, 1991). Clinical primary trichuriasis has been diagnosed in South Africa (Bowie *et al*, 1978; Sandler, 1981). Even symptomless trichuriasis can impair growth (Forrester *et al*, 1998). In children the syndrome includes :

- colitis and appendicitis (Neafie *et al*, 1976; Beaver *et al*, 1984; Bundy, 1986; Cooper *et al*, 1986; Cooper *et al*, 1987; Cooper & Bundy, 1988)
- leakage of blood cells, plasma and electrolytes from mucosal inflammation (Layrisse *et al*, 1967; Neafie *et al*, 1976; Cooper *et al*, 1997)
- anaemia (Layrisse *et al*, 1967; Beaver *et al*, 1984; Chanco, 1978; Stoltzfus *et al*, 1996)
- diarrhoea, dysentery and dehydration (Getz, 1945; Gilman *et al*, 1976; Gilman *et al*, 1983; Cooper *et al*, 1986; Bundy & Cooper, 1989)
- abdominal pain and depression (Beaver *et al*, 1984; Joo, 1998)
- severely retarded growth (Bowie *et al*, 1978; Cooper & Bundy, 1988; Cooper *et al*, 1990)
- impaired mental development which may be permanent (Cooper & Bundy, 1988; Callender *et al*, 1992; Callender *et al*, 1994; Callender *et al*, 1998)

Secondary disease can be subtle, complex and chronic, such as modulation of the immune system (Cooper *et al* 1991; Else & Grencis, 1991; Bentwich *et al*, 1999). The host confronted with the chronic burden of worms mounts a prolonged response to this challenge which could alter the normal immune balance. Such changes may also have profound effects on the ability to cope with other infections and affect the general and specific immune response to other stimuli (Bentwich *et al,* 1996; Bentwich *et al*, 1997; Fincham & Markus, 1999; Fincham *et al*, 1999), such as tuberculosis and HIV/AIDS. In both diseases the onset is slow and the pathogens are localised within immune cells so that they evade and suppress the host immune response (Bentwich *et al*, 1997; Bentwich *et al,* 1999; Fincham & Markus, 1999). Secondary disease can also be acute and dominant, such as when enteropathogenic bacteria, viruses and protozoa impose on inflammation originally due to trichuriasis (Jung & Beaver, 1951; Gilman *et al*, 1976; Muller, 1975; Gilman *et al*, 1983). Clear distinction between primary and secondary disease is not always possible because they merge and the secondary phenomena can be overwhelming. The combination expresses as morbidity, which may be subtle or overt, and affect individuals or populations.

Population morbidity is the most important effect of trichuriasis and other helminthic infection which are endemic, as opposed to epidemic. It is a reflection of prevailing human ecology in terms of hygiene, sanitation, clean food and water, occupational density inside dwellings and overall crowding. It is a component of public health, community health, environmental health, and health education, in terms of services and delivery. This places it into the ambit of **Essential National Health Research** in South Africa and many other developing countries. Morbidity due to trichuriasis and other helminth infections adds up to a major burden of disease on a population basis. Substantial analysis has been undertaken by Bundy *et al*, 1985a; Bundy *et al*, 1985b; Anderson, 1986; Bundy, 1986; Bundy *et al*, 1987; Bundy *et al*, 1992; Cooper *et al*, 1992; Booth *et al*, 1998; Guyatt, 2000.

It is necessary to use practical measures to assess morbidity. The consensus after analysis and debate, is that the main determinant of morbidity, or burden of disease, amongst the population as a whole, is the **prevalence** of trichuriasis and/or concomitant helminthic infection. This is valid for any mean intensity of infection or worm burden, and is summarised graphically in Fig. 10. The relationship of prevalence to population morbidity (Fig. 11) is the basis for the internationally accepted recommendation that when prevalence of geohelminthiasis is 50% or more, mass treatment programmes are necessary for all school-age children, because they harbour most of the worms in any community, as well as the most intense infection. Hookworm is an exception because prevalence peaks in adolescents and adults (Bundy *et al*, 1992; Bundy & de Silva, 1998; Schmidt & Roberts, 2000).

The main reason for the non-linear relationship of prevalence to population morbidity (Fig. 10) is because the number of worms per infected person is not uniformly or randomly distributed amongst all the people who are infected in a population, and is in fact highly aggregated or overdispersed (Anderson, 1986; Bundy *et al*, 1992; Booth & Bundy, 1995). In simple terms this means that most people do not have many worms, and a few people have a lot. This is why distribution curves of egg count frequencies and worm burdens are described by a negative binomial function, and are usually characterised by severe skewing towards lower egg counts. It is the minority of people who are heavily infected who contribute most of the eggs to the environmental contamination which perpetuates infection.

The characteristics of population morbidity described in the preceding paragraphs mean *inter alia* that it is much more effective, practical and cost beneficial to minimise and control morbidity, than try to eliminate infection in the whole community. In practice this means that it is the children who carry most of the worms, as well as the burden of disease, who should be treated regularly *en masse*, rather than all the people in the community.

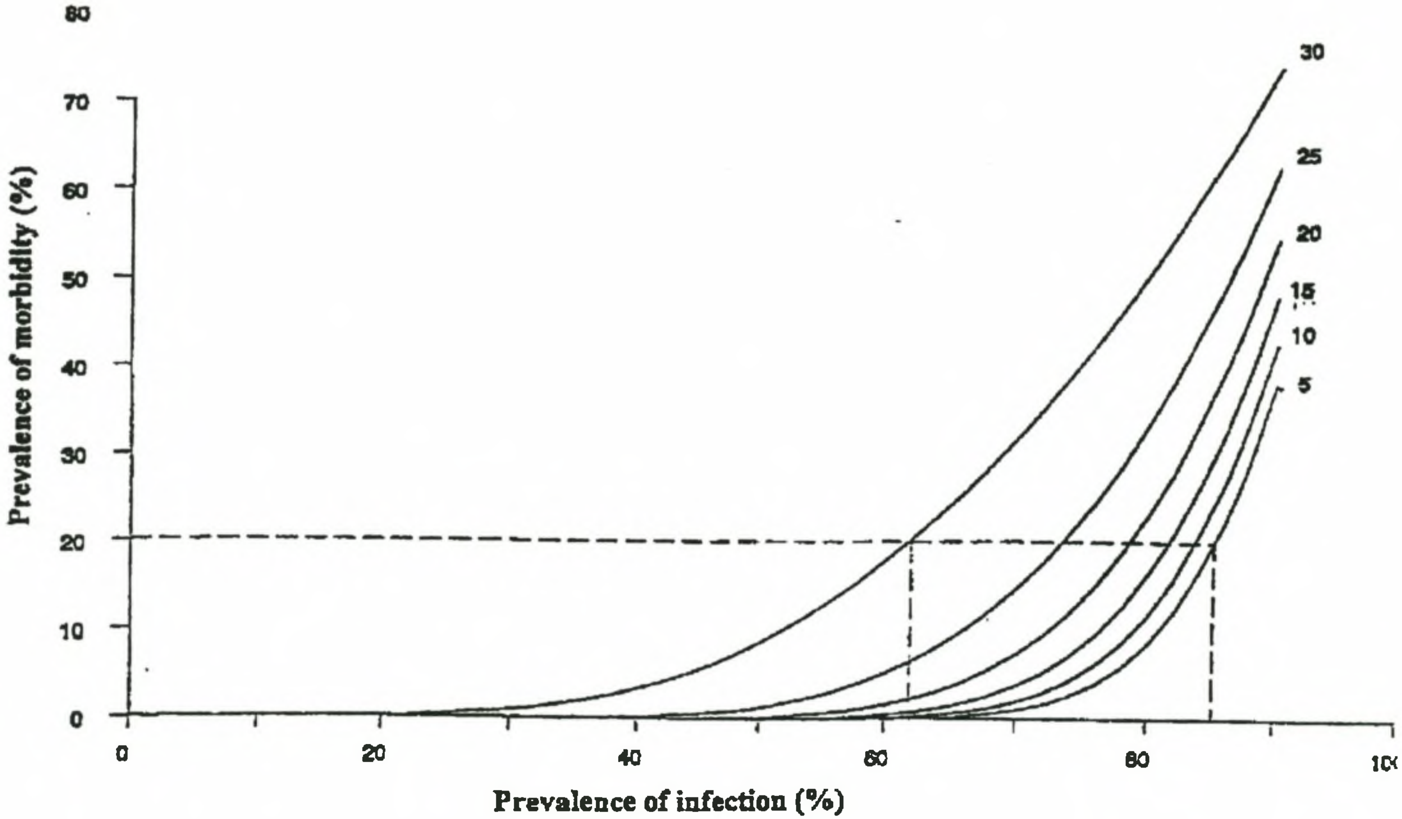

Fig. 10: The threshold of morbidity in a population or community (20%) is determined more by prevalence of infection, than by the mean worm burden, over the range of five to 30 worms (shown by numbers to the right of curved lines). This means that if people usually have few worms, but most people are infected, there will be significant morbidity over the whole population. Successful intervention can reverse this situation (modified from Bundy *et al*, 1992).

A unique epidemiological difference between the main helminth parasites of man, which are macroparasites, and the microparasites comprising bacteria, viruses and protozoa pertains to multiplication within the host (Bundy *et al*, 1992; Maizels *et al*, 1993). Although male and female helminths reproduce sexually within the host, there is no *in situ* multiplication because eggs are passed out in the faeces and must undergo further development to become infective. Two exceptions to this are specified below. In contrast, the microparasites multiply within the host rapidly and asexually, sometimes at a generation interval of minutes. This means that infection by a single microparasite pathogen can soon be overwhelming. The only way in which massive infection by geohelminths can arise is by ingestion of large numbers of eggs from the environment. Hence the importance of preventing exposure to environmental contamination by human faecal material, and the great potential for control of disease in ways which are simple and practical. This fundamental situation is often not understood. Moreover, by cleaning environments of faeces containing helminth eggs, the risk of infection by other enteropathogens in faecal contamination, is automatically reduced.

The better-known helminth which does multiply within the human hosts is *Strongyloides stercoralis*. Primary infection follows ingestion of eggs. Hyperinfection develops in immunosuppressed people in particular, because eggs hatch before they are passed in stools, and the larvae autoinfect. They reach multiple organs and this type of infection can be lethal (Beaver *et al*, 1984; Walden, 1991; Lui & Weller, 1993; Hacque, 1994; Gomes-Moralez, 1995). The lesser-known helminth which can multiply within humans is *Capillaria phillipensis*. Fish-eating birds are the usual definitive host, with fish the intermediate host. Humans are infected by eating raw fish. Female worms in the human intestine produce eggs and free larvae. The latter can autoinfect to increase severity of infection in the original host (Cross, 1992).

Recent local results in comparison to some aspects of conventional epidemiological theory.

Four surveys of prevalence and intensity of helminthiasis in substantial numbers of children at primary schools in the Western Cape Province of South Africa have been completed by the author since 1996 (Table 7). These concur with conventional epidemiological theory regarding severe skewing of egg counts because the geometric means are similar to the medians, but both these parameters are distinctly different from the arithmetic means. In terms of magnitude, the arithmetic means exceed the GM's by multiples of four to eight times.

Table 7: Descriptive statistics for egg counts in three groups of primary school children

Community	n	*Geometric mean	*Median	*Arithmetic mean
Khayelitsha	316	1566	1559	12563
Rawsonville	462	41	83	671
Langebaan North	300	196	240	1502
Uitsig	1940	15	9	444
Ravensmead	2128	7	0	224

Author's unpublished results.

* The arithmetic mean bears no resemblance to the medians or geometric mean which are similar, because distribution of egg counts is severely skewed by overdispersion or aggregation.

Uitsig is a suburb of Cape Town where the incidence of tuberculosis is exceptionally high and people are poor (Beyers *et al*, 1996; Adams *et al*, 1999). In this community the peak of age-related prevalence of trichuriasis was in fourteen year old children (Table 8 and Fig. 11). This is substantially older than the ages described in West Indian studies on which much of the conventional epidemiology is based (Anderson, 1986; Bundy *et al*, 1992; Booth & Bundy, 1995). In the baseline survey of 462 children at Rawsonville Primary School, the prevalence peaked in children who were 12 years old. This also does not conform with the theory. However, it is not possible to give this statistic for the Khayelitsha children because birth dates were not accurately known. Results from a large survey in China also show that prevalence of *Trichuris* can peak in teenage children (Long-Qi *et al*, 1995).

Table 8: Number of children tested per age group in four schools in Uitsig.

Age (years)	**<6**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15+**
# tested	8	184	196	260	245	230	222	205	214	86	41
# infected	1	99	93	139	128	134	135	119	124	64	21
% infected	12.5	53.8	47.4	53.5	52.2	58.3	60.8	58	57.9	74.4	51.2

Author's unpublished results.

Finally, the initial survey of children in Khayelitsha demonstrated clear variation from the convention that intensity is highly overdispersed towards low egg counts (Fig. 12). The Rawsonville distribution does conform because 60.7% of children had less than 1000 epg of faeces **(black bars)**. This is called overdispersion and the curve is described by a negative binomial function (Anderson, 1986; Bundy *et al*, 1992; Booth & Bundy, 1995). However, the frequency distribution for Khayelitsha does not conform to the dispersion perceived as typical **(red bars)**. Twenty five percent of Khayelitsha children had more than 10 000 epg. The whole frequency distribution was therefore not overdispersed towards low egg counts, and could not be described mathematically by a negative binomial function.

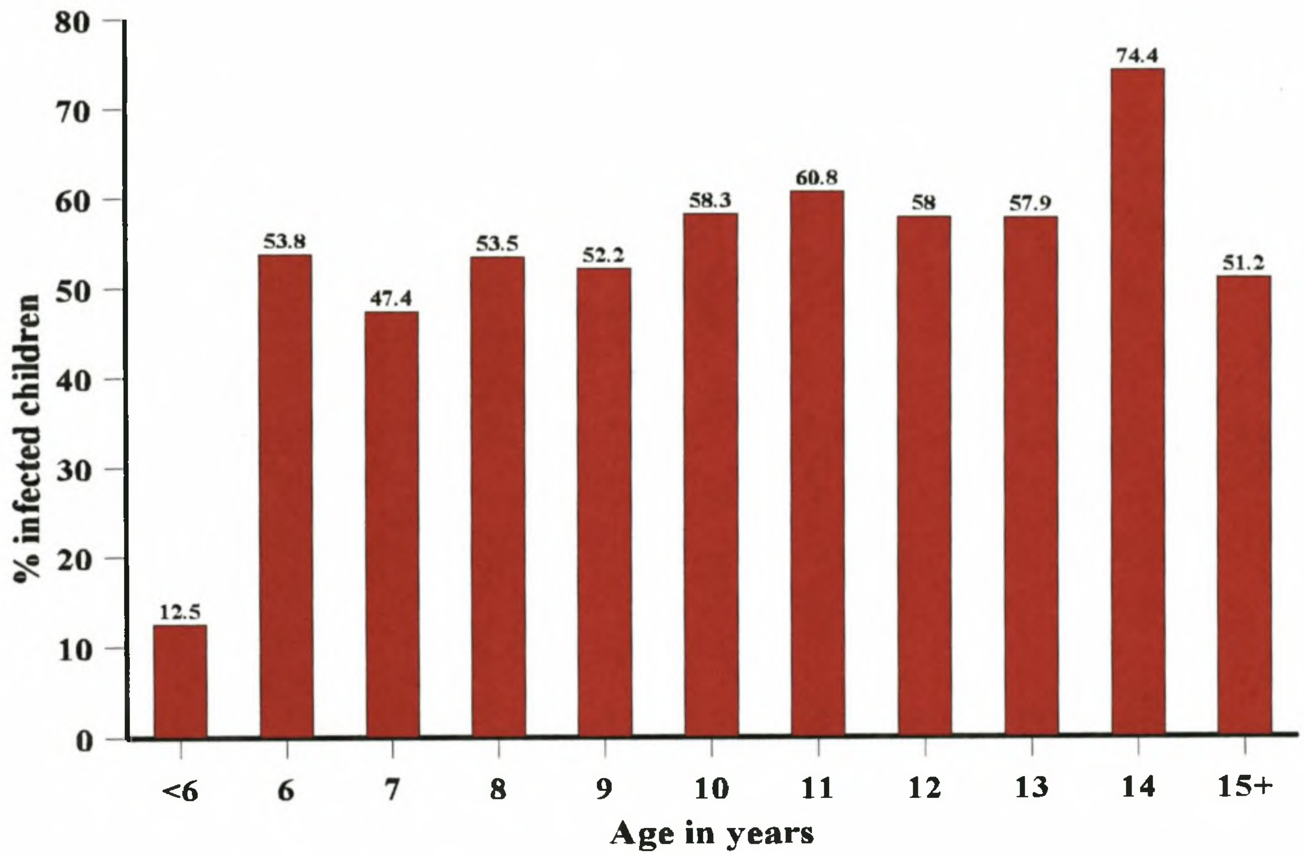

Fig. 11: Age-related prevalence of trichuriasis in four primary schools in Uitsig, a socio-economically disadvantaged suburb of Cape Town. There was little difference between boys and girls. See Table 8 for numbers in each age bar (Author's unpublished results, 1999).

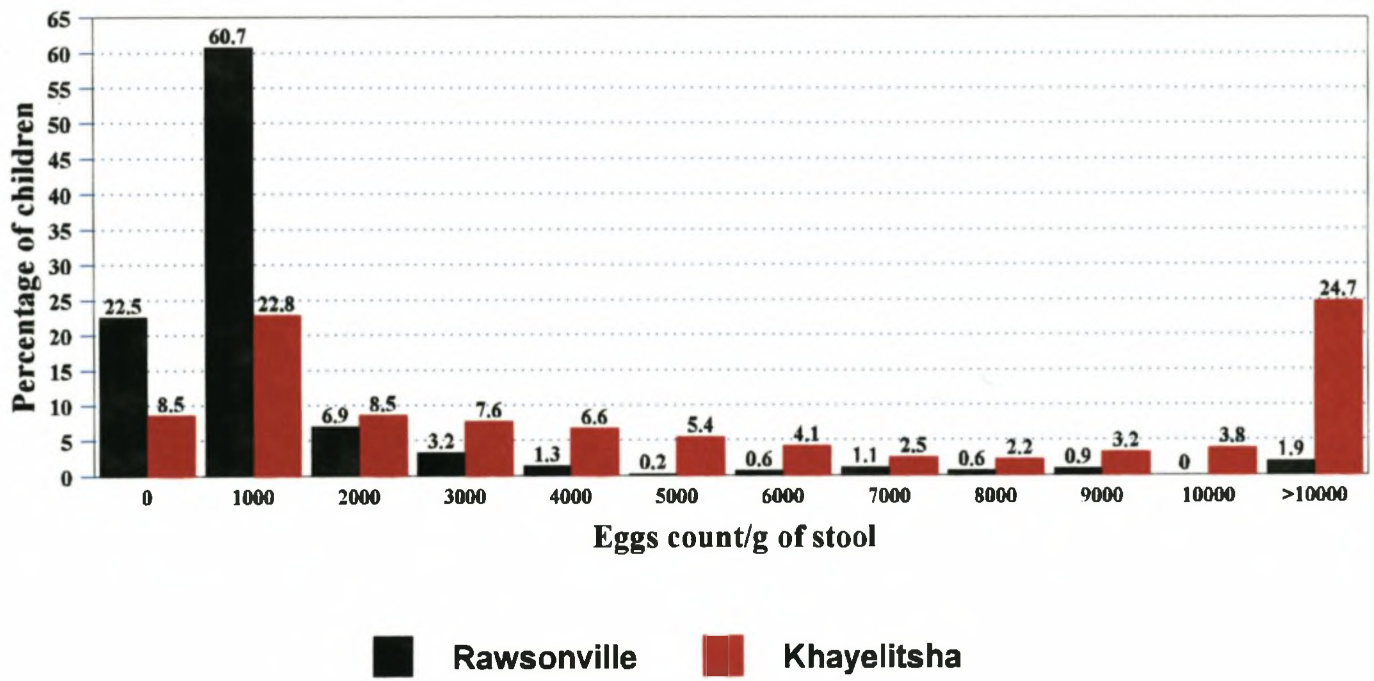

Fig. 12: The frequency distribution of egg counts in Rawsonville conforms to conventional epidemiology, but that for Khayelitsha does not. See text (Author's unpublished results, 1997).

CHAPTER 4

The effect of three different doses of albendazole, each repeated four times, on *Trichuris trichiura* infection in primary school children: A Randomised Controlled Trial

Albendazole is a benzimidazole anthelmintic that was first approved for treatment of helminth infections in sheep in 1977 (de Silva *et al*, 1997). It was approved for use in humans in 1983 and in 1998 it was still protected by patent and no generics were available. Like mebendazole it exerts most of its anthelmintic activity directly in the lumen of the intestine, but plasma concentrations are substantially more than for mebendazole, i.e. 15 to 49 times greater (de Silva *et al*, 1997). After absorption it is converted rapidly in the liver to albendazole sulpoxide, which is the primary metabolite and also has anthelmintic activity. Recommended doses for geohelminths are either 400 mg stat or repeated daily for three days in heavy mixed infections. The stat dose facilitates compliance in sustained deworming programmes but is generally less effective than when treatment is repeated daily for three days. Albendazole is used at higher doses for treatment of strongyloidiasis, hydatid disease, neurocysticercosis, cutaneous larva migrans and visceral larva migrans (SAMF, 2000). It has also been used in chronic diarrhoea associated with AIDS with some success (Kelly *et al*, 1996), and may have activity against intestinal protozoa like *Giardia duodenalis* (Misra *et al*, 1995; Penggabean *et al*, 1998; Reynoldson *et al*, 1998; Pengsaa *et al*, 1999).

After very high dosage albendazole was teratogenic in rats and rabbits (de Silva *et al*, 1997). Therefore it should not be used in the first trimester of pregnancy.

In 1994, a study to assess infection by intestinal parasites and nutrition was undertaken by the Medical Research Council (MRC) at five primary schools situated in Worcester, De Aar and Rawsonville, in the Boland/Overberg Health Region (Fig. 14). Results of this study showed that 58.7% (91/155) of children were infected by intestinal parasites. At Rawsonville Primary School prevalence increased to 90% (Kruger *et al*, 1996). *Trichuris* was a component of 65% of the infections. Results also showed that children infected by *Trichuris* were significantly more anaemic and iron depleted than uninfected children. Within the limitations of study design, significant positive effects on haemoglobin and growth after two anthelmintic treatments were reported. However, prevalence of *Trichuris* was not clearly reduced. Definition of an effective treatment programme for *Trichuris* under local conditions was therefore necessary, especially considering the potential for resistance to anthelmintic treatment (WHO, 1998a; WHO, 1998b; Bennet & Guyatt, 2000).

The main objective of the randomised controlled trial (RCT) now reported, was to identify an effective albendazole dose for the treatment of *T. trichiura* in the Western Cape in communities where whipworm is the predominant infection. Other studies currently in progress are evaluating the efficacy of mebendazole. WHO recommends a single 400 mg albendazole dose (WHO, 1998a). Several publications have noted that a single 400 mg dose of albendazole is not effective in producing high CR for *T. trichiura* (Kan, 1983a; Ramalingam *et al*, 1983; Rossignol & Maisonneuve, 1983; Ow-Yang & Hanjeet, 1986; Chen *et al*, 1990; Ismail *et al*, 1990; Hanjeet & Mathias, 1991; Bartloni *et al*, 1992; Hall & Nahar, 1994; Marti *et al*, 1996; WHO, 1996). Other studies have found that a single 400 mg albendazole dose was sufficient to produce CR of up to 100% (Misra *et al*, 1985; Jagota, 1986). Another factor that needs to be taken into account is the fact that geographical locations and season of the year appear to influence CR (Albonico *et al*, 1999; Bennett & Guyatt, 2000). It is also therefore imperative that the efficacy of any anthelmintic be tested for different regions and seasons.

Study population

Rawsonville Primary School is situated in the town of Rawsonville about 90 km east from Cape Town, in the Boland/Overberg Health Region (Fig. 13). The majority of children attending this school live on the surrounding wine farms and 77% of the children enrolled in the RCT were from farms. The Region is well known for the wine it produces. Farmers provide housing for their workers and their families and conditions of housing differ from farm to farm. Some houses have electricity while others use gas or burn wood. There are adequate toilet facilities on some while on other farms pit latrines are still used. Most of the houses do not have their own toilet and more than one family usually share a toilet. This leads to many people defecating in the environment surrounding the houses. Communal taps are also in use. The children attending this school are regarded as being disadvantaged and the Peninsula School Feeding Association (PSFA), an organisation devoted to the feeding of hungry and underprivileged children in primary schools throughout the Western Cape, provides a light meal during school (Fig. 14)

Fig. 13: The position of the Boland/Overberg Health Region in relation to other Health regions in the Western Cape Province of South Africa.

Fig. 14: Children at Rawsonville Primary School enjoying food supplied by the Peninsula School Feeding Association.

Study design

A double blinded, randomised controlled trial was used to test for an effective dose of albendazole (*Zentel*®, SmithKline Beecham) against *T. trichiura*. Blinding was achieved in several ways. The albendazole and placebo tablets were identical, including the packaging. Neither the person administering treatment, nor the child receiving treatment, was aware of the dose. Faecal samples were coded and microscopists in the laboratory were not aware which treatment group samples pertained to. Researchers broke the code at the end of the study in order to analyse data in relation to treatments. All the raw data are in the files of the Medical Research Council. Preliminary procedures that were necessary to implement the RCT, are described in the paragraphs that follow.

After understanding that the trial would be beneficial to child, school and community health, the parent or guardian of each participant signed a consent form (Appendix 1). The study was approved by the Ethics Committee of the MRC. Permission was also obtained from the Department of Education via the Principal of the school.

In a baseline survey, faecal samples from 462 children ranging in age from six to 16 years (mean 10 years), were assessed using the formal-ether concentration technique (Ash, 1991; WHO, 1994). Helminth eggs were counted and expressed quantitatively as eggs per gram (epg) of stool. Seventy seven percent of the children had worm eggs in their stool, with 69% infected with *T. trichiura*, 34% with *Ascaris lumbricoides*, and 26% were infested by both these worms. Eight percent of children had *Ascaris* but no *Trichuris*. The classes of intensity for *T. trichiura*, as defined by Montresor *et al* (1998) are summarised in Table 9.

Table 9: Intensity of infection according to WHO criteria* for *Trichuris* egg counts per g of faeces (epg) amongst 462 children in the baseline sample.

Intensity	Zero	Light	Moderate	Heavy
Epg	0	1 - 999	1 000 - 9 999	≥ 10 000
Children (%)	143 (31)	258 (56)	57 (12)	4 (<1)

*Montressor *et al*, 1998

One hundred and fifty children were selected for treatment with albendazole, from the baseline sample, using the criteria of maximising *Trichuris* epg of stool and inclusion in supplementary feeding provided by PSFA. Children on chronic prescription medication and/or with clinical abnormalities were excluded by the MRC pediatrician in attendance. Seventy five boys with the highest epg, ranging between 350-8 200 epg, as well as 75 girls with epg's ranging between 320-32 760 were selected. The 150 selected children were each identified by a unique numerical code and allocated to three cohorts using random permutations in blocks of three. An impartial statistician found no significant imbalances in terms of egg counts, ages, length-for-age and weight-for-age (WHO, 1995) between the cohorts. The mean age of the selected children was nine years and the range was six to sixteen years. The three groups were then randomised to the different doses of albendazole (Table 10). An additional cohort of 50 uninfected children (i.e. no worm eggs in faecal sample) was also selected with treatment with placebo. This was done because the inclusion of an orthodox randomised control group was prevented by a directive from the ethics committee, forbidding placebo treatment of children known to have worms. Therefore, the children treated with placebo were a reference or negative control group.

Table 10: Treatments over three days, repeating at four months intervals.

Treatments	**Day 1**	**Day 2**	**Day 3**
Placebo	Placebo	Placebo	Placebo
Albendazole* 400 mg	400 mg	Placebo	Placebo
Albendazole* 800 mg	400 mg	400 mg	Placebo
Albendazole* 1200 mg	400 mg	400 mg	400 mg

******Zentel*®** SmithKline Beecham, 400 mg tablets**

Blister packs and tablets of albendazole and placebo matched exactly and were prepared in the SmithKline Beecham factory in France. *Zentel*® is the trademark used by SmithKline Beecham for their formulation of albendazole. In the laboratory, sets of three blister packs for each coded recipient, were prepared. Within each coded set, the three blister packs were marked for the child concerned, and for day 1,2 or 3, respectively (Fig. 15). At school, administration of each set to the corresponding child was double blind (Fig. 16).

Fig. 15: Researcher preparing treatment sets of tablets in the laboratory.

Fig. 16: Teacher providing tablets from identical sets to corresponding pupils (Table 10). Neither the teacher nor the child knew whether tablets were placebo or albendazole.

Methods and Management

A field manager and two assistants, who were all members of the community, were trained to work with the children. This included administrative duties such as distributing the tablets to the correct classes so that teachers could treat the children, weighing and measuring children and co-ordination of collection of faecal samples. The field manager was also responsible for following up on any children who were absent on the day of treatment.

1 Collection of stool samples

Containers for faecal samples were new, sterile and of 30 ml capacity with threaded tops. A new, sterile, wooden spatula was placed inside each of these, for manipulating a portion of fresh stool in the container. The children were instructed to return the container at least half filled. Faecal samples were collected immediately before each anthelmintic treatment and again about one month after treatment. Determination of egg counts within a month after treatment will give an indication of the efficacy of the drug, by means of cure rate (CR) and egg reduction rate (ERR), which reflects intensity of infection. Decreases in CR and ERR, especially the latter, are recognised as early indicators of resistance to anthelmintic (WHO, 1998a; Bennett & Guyatt, 2000). Faecal sampling again, immediately before the next treatment, allowed us estimation of the reinfection rate.

2 Laboratory analysis of stool samples

A temporary laboratory was set up at the school for receipt and initial processing of faecal samples by the field manager and the assistants. Upon collection, the samples were homogenised, a sample size of between 0.5 - 1.0 g was weighed out and the consistency (or density) was graded (Table 11). This enables a multiplication factor for the different consistencies to be applied to the egg counts to make them more comparable (Archer *et al*, 1997). Individual sample weights and multiplication factors were recorded on data sheets. Each homogenised faecal subsample was fixed in ± 4 ml of 10% formalin and stored in a bijou bottle.

Table 11: Stool consistency factors used to adjust egg counts.

Stool Consistency	Multiplication Factor
Formed (F)	Egg count x 1.0
Semi-formed (SF)	Egg count x 1.5
Mushy (M)	Egg count x 2.0
Mushy-diarrhoea (MD)	Egg count x 3.0
Diarrhoea (D)	Egg count x 4.0
Watery (W)	Egg count x 4.5

Further processing and microscopy was according to standard methods (Ash & Orihel, 1991; WHO, 1994). Egg counts were expressed quantitatively per 1 g of faeces according to the following formula;

Number of eggs/g = (Egg count)(consistency factor)/weight of sample in g

3 Evaluation of laboratory results

Statistical methods were necessary to interpret cure rates achieved by the respective doses of albendazole. These are explained in the text which follows. Results for egg reduction rates and some suggestive evidence for resistance to albendazole, did not require statistical methods according to a statistical consultant, because these results were not equivocal. Cure rates for each dose of albendazole and particular treatment occasion, after the initial 100% prevalence of *Trichuris*, and after the effect of the first treatment, were analysed within treatment groups by McNemar's chi-squared analysis (MN). In order to apply this method, 2 x 2 lattices were constructed for results relating to each dose of albendazole (Tables 12.1 - 12.3). The marginal values of these lattices were analysed. Data for each occasion was transformed to binary outcome, so that egg positives were coded as one (1) and egg negatives as zero (0).

Confirmation of the McNemar results was sought by the Jonckheere-Terpstra test (JT), and by linear repeated measures analysis (LRM) (Grizzle, 1969; Wilson & Grenfell, 1997). The JT test is a non-parametric one-way analysis of variance that is more specific than the standard Kruskal Wallis method. The JT test was also used to test the hypothesis of a dose effect, versus the null hypothesis of no effect, in terms of GM egg counts on each treatment or non-treatment occasion. There were four treatment occasions and three non-treatment occasions, a total of seven observational points. Possible confounding of cure rates due to dose of albendazole and time (season) was included in the analysis. Gender was not considered because there is no known reason why girls and boys should respond differently to oral treatment with albendazole.

LRM analysis was applied to binary outcomes as for the MN test, in the CATMOD procedure of SAS. Three models were possible, based on the treatment and non-treatment occasions, and combination of both. The models permit a graphical display of predicted vs observed rates of cure and reinfection.

Cure rate on the treatment occasions with 400 mg albendazole(a)

	Original	Rx 1 changes			Rx 2 changes			Rx 3 changes			Rx 4 changes		
Pos	31	23		27	23	4	26	24	2	23	22	1	
Neg	0		8	4	0	4	5	2	3	8	2	6	
	31	23	8	31	23	8	31	26	5	31	24	7	31
		Pos	Neg		Pos	Neg		Pos	Neg		Pos	Neg	

Pos = the number of children with eggs of *Trichuris trichiura* in the faecal sample. Neg = the number of children with no *Trichuris trichiura* eggs in faecal sample. Yellow squares = 2 x 2 lattice. Green squares = marginal outcomes.

Changes between treatments (non-treatment occasions) due to reinfection (b)

	After Rx 1	Pos	Neg	After Rx 2	Pos	Neg	After Rx 3	Pos	Neg	
Pos	23	22	1	23	23	0	26	23	3	
Neg	8	5	3	8	3	5	5	0	5	
	31	27	4	31	26	5	31	23	8	31

Pos = the number of children with eggs of *Trichuris trichiura* in the faecal sample. Neg = the number of children with no *Trichuris trichiura* eggs in faecal sample. Yellow squares = 2 x 2 lattice. Green squares = marginal outcomes.

Table 12.1: Arrangement of data for McNemar's chi-squared analysis. The 2 x 2 lattice values (coded yellow) are results in terms of number of children who were positive or negative for eggs of *Trichuris trichiura* on specific occasions. Green coded squares contain the marginal outcomes of the lattice. These were used to evaluate effects due to treatment, non-treatment, dose of albendazole and season. Statistical methods were McNemar's chi-squared test, the Jonckheere-Terpstra test and linear repeated measures analysis.

Cure rate on the treatment occasions with 800 mg albendazole given as 400 mg on successive days (a)

	Original	Rx 1 changes			Rx 2 changes			Rx 3 changes			Rx 4 changes		
Pos	43	23		30	22	8	32	25	7	26	16	10	
Neg	0		20	13	1	12	11	2	9	17	3	14	
	43	23	20	43	23	20	43	27	16	43	19	24	43
		Pos	Neg		Pos	Neg		Pos	Neg		Pos	Neg	

Pos = the number of children with eggs of *Trichuris trichiura* in the faecal sample. Neg = the number of children with no *Trichuris trichiura* eggs in faecal sample. Yellow squares = 2 x 2 lattice. Green squares = marginal outcomes.

Changes between treatments (non-treatment occasions) due to reinfection (b)

	After Rx 1	Pos	Neg	After Rx 2	Pos	Neg	After Rx 3	Pos	Neg	
Pos	23	20	3	23	21	2	27	24	3	
Neg	20	10	10	20	11	9	16	2	14	
	43	30	13	43	32	11	43	26	17	43

Pos = the number of children with eggs of *Trichuris trichiura* in the faecal sample. Neg = the number of children with no *Trichuris trichiura* eggs in faecal sample. Yellow squares = 2 x 2 lattice. Green squares = marginal outcomes.

Table 12.2: Arrangement of data for McNemar's chi-squared analysis. Treatment with 800 mg albendazole. The 2 x 2 lattice values (coded yellow) are results in terms of number of children who were positive or negative for eggs of *Trichuris trichiura* on specific occasions. Green coded squares contain the marginal outcomes of the lattice. These were used to evaluate effects due to treatment, non-treatment, dose of albendazole and season. Statistical methods were McNemar's chi-squared test, the Jonckheere-Terpstra test and linear repeated measures analysis.

Cure rate on the treatment occasions with 1200 mg albendazole given as 400 mg on successive days (a)

	Original	Rx 1 changes			Rx 2 changes			Rx 3 changes			Rx 4 changes		
Pos	39	18		17	13	4	23	12	11	17	11	6	
Neg	0		21	22	5	17	16	0	16	22	2	20	
	39	18	21	39	18	21	39	12	27	39	13	26	39
		Pos	Neg		Pos	Neg		Pos	Neg		Pos	Neg	

Pos = the number of children with eggs of *Trichuris trichiura* in the faecal sample. Neg = the number of children with no *Trichuris trichiura* eggs in faecal sample. Yellow squares = 2 x 2 lattice. Green squares = marginal outcomes.

Changes between treatments (non-treatment occasions) due to reinfection (b)

	After Rx 1	Pos	Neg	After Rx 2	Pos	Neg	After Rx 3	Pos	Neg	
Pos	18	13	5	18	16	2	12	11	1	
Neg	21	4	17	21	7	14	27	6	21	
	39	17	22	39	23	16	39	17	22	39

Pos = the number of children with eggs of *Trichuris trichiura* in the faecal sample. Neg = the number of children with no *Trichuris trichiura* eggs in faecal sample. Yellow squares = 2 x 2 lattice. Green squares = marginal outcomes.

Table 12.3: Arrangement of data for McNemar's chi-squared analysis. Treatment with 800 mg albendazole. The 2 x 2 lattice values (coded yellow) are results in terms of number of children who were positive or negative for eggs of *Trichuris trichiura* on specific occasions. Green coded squares contain the marginal outcomes of the lattice. These were used to evaluate effects due to treatment, non-treatment, dose of albendazole and season. Statistical methods were McNemar's chi-squared test, the Jonckheere-Terpstra test and linear repeated measures analysis.

Explanation of how the data arrangement in Tables 12.1 - 12.3 was obtained, is necessary. To assess cure rate (CR) on four treatment occasions, a faecal sample was obtained just before a treatment and followed up within a month after treatment. This procedure ensured that *Trichuris* eggs from reinfection did not reduce CR since it takes at least three months for eggs to appear in faeces (Beaver *et al*, 1984; Horri & Usuii, 1985; Schmidt & Roberts, 2000). These results are in lattice blocks (a) of Tables 12.1 - 12.3.

Changes during three intermediate non-treatment occasions when eggs from re-infection and new infection could appear in faeces, were also assessed. These results are shown in the lattice blocks (b) in each of Tables 12.1 - 12.3.

To clarify analysis of CR during treatment occasions, consider the block for the changes due to the second treatment in Table 12.1, which is extracted below as Table 13.

Table 13: Analysis of cure rate by the second treatment of 400 mg albendazole.

	Rx 2 changes			
		Pos	**Neg**	
Pos	27	23	4	26
Neg	4	0	4	5
	31	23	8	31

Extracted from Table 12.1. See text.

The marginal values in the green squares to the left were the number of children who were positive or negative for eggs, respectively, immediately before the second treatment. Deworming cured four positives, resulting in marginal totals of 23 and eight below the yellow columns. The cure rate for the specific treatment was 4/27, or 14.8%. The cumulative CR from 100% infection at baseline was 8/31, or 25.8%. Note that the marginal values before the third treatment, shown in the green column to the right, changed during the intermediate non-treatment occasion, to 26 positives and five negatives. This was due to reinfection of three negatives. Loss of infection due to natural death of the parasitic worm can also occur, such as before the last treatment in Table 12.1. Reinfection in the non-treatment occasions was analysed in a similar manner using the lattice blocks (b) of Tables 12.1 - 12.3.

4 Anthropometry

The height and weight of each child was monitored by standardised methods. Before weighing it was necessary to ensure that pupils wore the minimum of clothing. Shoes and socks were removed. Elevated hair arrangements of some girls were loosened. The weight to the nearest 0.1 kg was taken using a calibrated electronic scale. The same scale was used throughout the study. Standing height without shoes was measured with a portable length measuring device consisting of a wooden board on which a measuring tape was permanently fixed and a sliding head piece. Height was measured to the nearest 0.1 cm and the same measuring board was used throughout the study. Birth date was obtained from the official school registers and used to calculate age. Height-for-age and weight-for-age z-scores were obtained from the computer software package ANTHRO Version 1.01 from the division of Nutrition, Centers fro Disease Control, Atlanta, USA, in collaboration with the Nutrition Unit, WHO. A child was classified as stunted when he/she had a height-for-age z-score of < -2 SD and as underweight when weight-for-age z-score was < -2 SD (WHO, 1995).

5 Haematology

Blood was drawn from the antecubital vein of each child and aliquoted into tubes containing ethyldiaminetetraacetic acid (EDTA) for anticoagulation. Differential white blood cell counts were obtained by means of a Technicon H2 Blood cell analyser (Technicon, Tarrytown, New York, USA). Counts which exceeded normal ranges were checked by microscopy. The laboratory reported results in relation to the date of birth, but had no other specific knowledge of the case. It was necessary to relate eosinophil counts to age because paediatric counts are physiologically higher than those of adults.

Results & Discussion

Children who left the school reduced the numbers from the original 50 children per treatment group (Table 14).

Table 14: Numbers in treatment groups at start and the end of the RCT.

Treatment group	Total at start	Total at end
400 mg	50	31
800 mg*	50	43
1200 mg*	50	39
Negative control**	50	32
Total	200	145

*Given as 400 mg/day on successive days

**Treated with placebo

es such as the RCT described in this thesis, CR reflects pharmacological nintic, or whatever drug is under test (see "Literature specific to efficacy of ter 2, page 47.) This in turn is linked to final drug quality or impairment nass production. For example, polymorph C mebendazole is an effective nolecule as polymorph A is useless (Charoenlarp *et al*, 1993). If CR's for an to decline, it may indicate development of resistance by the helminth under f resistance depends on measurement of reduced **egg reduction rates (ERR)** ctions in this chapter on ERR and on anthelmintic resistance), and finally on under controlled conditions (WHO, 1998a; Bennet & Guyatt, 2000).

oring CR is to check the effectiveness of mass deworming programmes The medication must be acceptable to those who should take it, in terms of objectionable side effects, and the programme must be able to deliver the rding to the treatment schedule, to be effective.

he three doses of albendazole, relative to 100% infection by *Trichuris* before able 15. These rates are cumulative and are not the specific result for each be seen by scrutiny of the marginal values in Table 12.1 - 12.3. The reason nfection during non-treatment occasions sometimes increased the number of ext treatment, as explained above.

Table 15: Cure rates (%) of the different treatment groups relative to baseline.

Rx Group	Baseline epg	n	After 1 Rx	After 2 Rx	After 3 Rx	After 4 Rx
400 mg	100	31	25.8	25.8	16.1	22.6
800 mg*	100	43	46.2	46.5	37.2	55.8
1200 mg*	100	39	53.8	53.8	69.2	66.7

*Given as 400mg on successive days

Trichuris CR's after 400 mg albendazole in tropical parts of Asia, where intensity of infection is usually higher than in non-Asian countries, have averaged 33.3% compared to 61% elsewhere. Notably, the CR's after the 400 mg dose at Rawsonville, did not achieve the Asian average, whereas those for the 800 and 1200 mg doses exceeded it, and they approached or exceeded the CR elsewhere (Bennett & Guyatt, 2000).

The influence of the cumulative CR's of the three doses of albendazole on residual prevalence in each treated group, is shown graphically in Fig. 17.

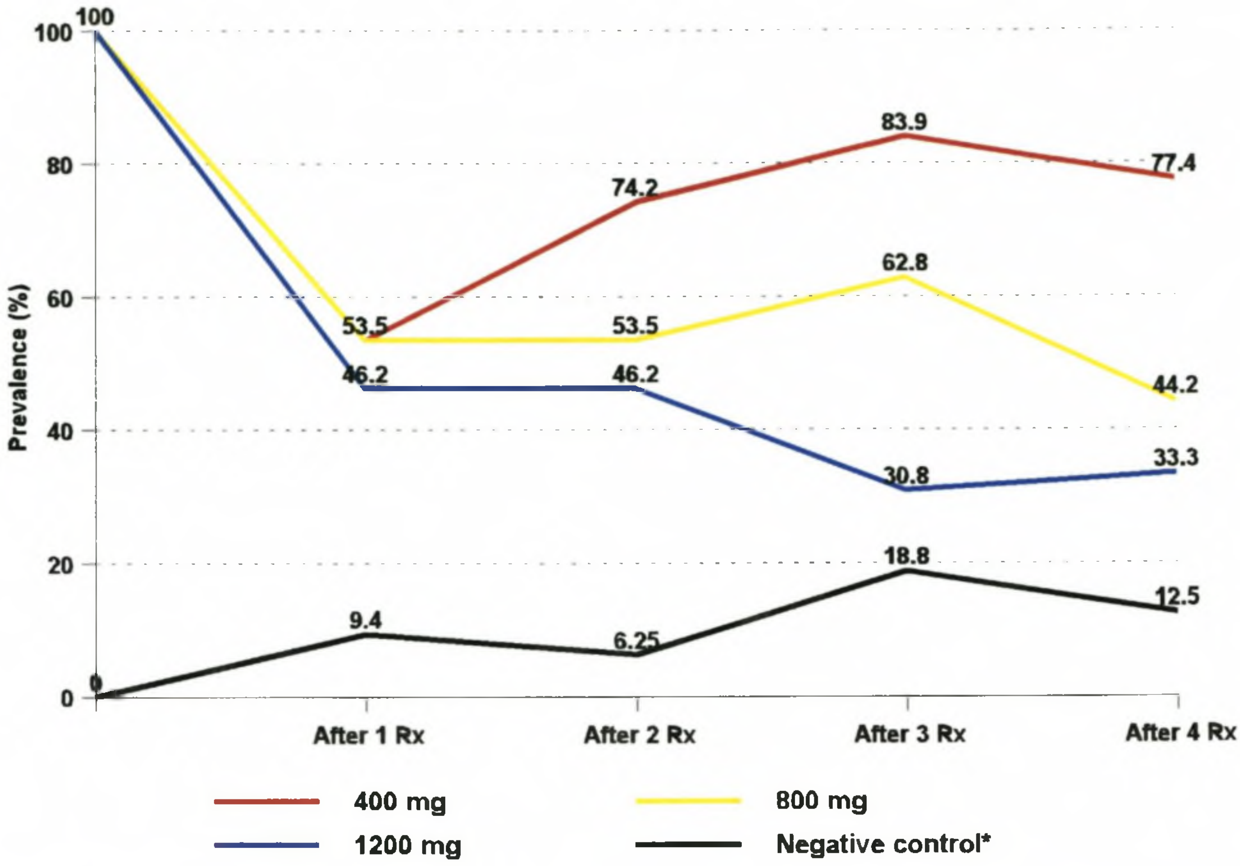

Fig. 17: Prevalence of *Trichuris trichiura* at baseline and after each of four albendazole treatments. The influence of reinfection was excluded by analysing faecal samples less than a month after each treatment.

The dose effect was very clear and regular treatment at intervals of approximately four months maintained the level of cure, but did not increase it. CR's after the 800 and 1200 mg doses were similar and significantly better than the 400 mg dose on every treatment occasion. Statistical results are summarised in Table 16. The similar CR's after the 800 and 1200 mg doses may be due to lack of statistical power. Use of larger groups of children in the groups could elucidate this.

Table 16: Significant differences between cure rates for the different doses of albendazole ($p<0.05$).

	Occasions		
Statistical test	**After Rx 1 & 2**	**After Rx 3**	**After Rx 4**
[1]JT occasions (T & NT)	See[3]	See[3]	0.0005
[1]LRM (400 vs 1200 mg)	0.0001[4]	0.0001[4]	0.0001[4]

[1]JT = Jonckheere - Terpstra. LRM = linear repeated measures

[2]T = on all treatment occasions, the higher doses achieved greater CR's than the 400 mg dose.

[3]T & NT: Three models are possible based on treatment (T), non-treatment (NT) and the combined occasions (T + NT). Results were similar and the combined model is recommended.

[4]CR for the 800 mg dose was similar to that for the 1200 mg dose. This might be due to the lack of statistical power, as explained in the text. Data converted to binary outcomes: 1 = egg positive; 0 = egg negative (see text).

LRM modelling over all occasions estimated that the 400 mg dose cured 21% (±SE 4) fewer children than the 1200 mg dose ($p = 0.0001$) (Table 16). The model confirmed that after the initial significant but differential effect of the three treatments, continuation maintained CR but did not increase it. The CR's for the 800 mg and the 1200 mg doses were similar.

LRM analysis for all occasions showed a non-significant residual effect ($p = 0.0664$) after controlling for dose ($p < 0.0001$), treatment ($p = 0.0011$), non-treatment ($p < 0.0001$) and interaction between treatment x non-treatment occasions ($p = 0.0460$). This validated comparison of predicted CR's and reinfection rates with actual results (Fig. 18).

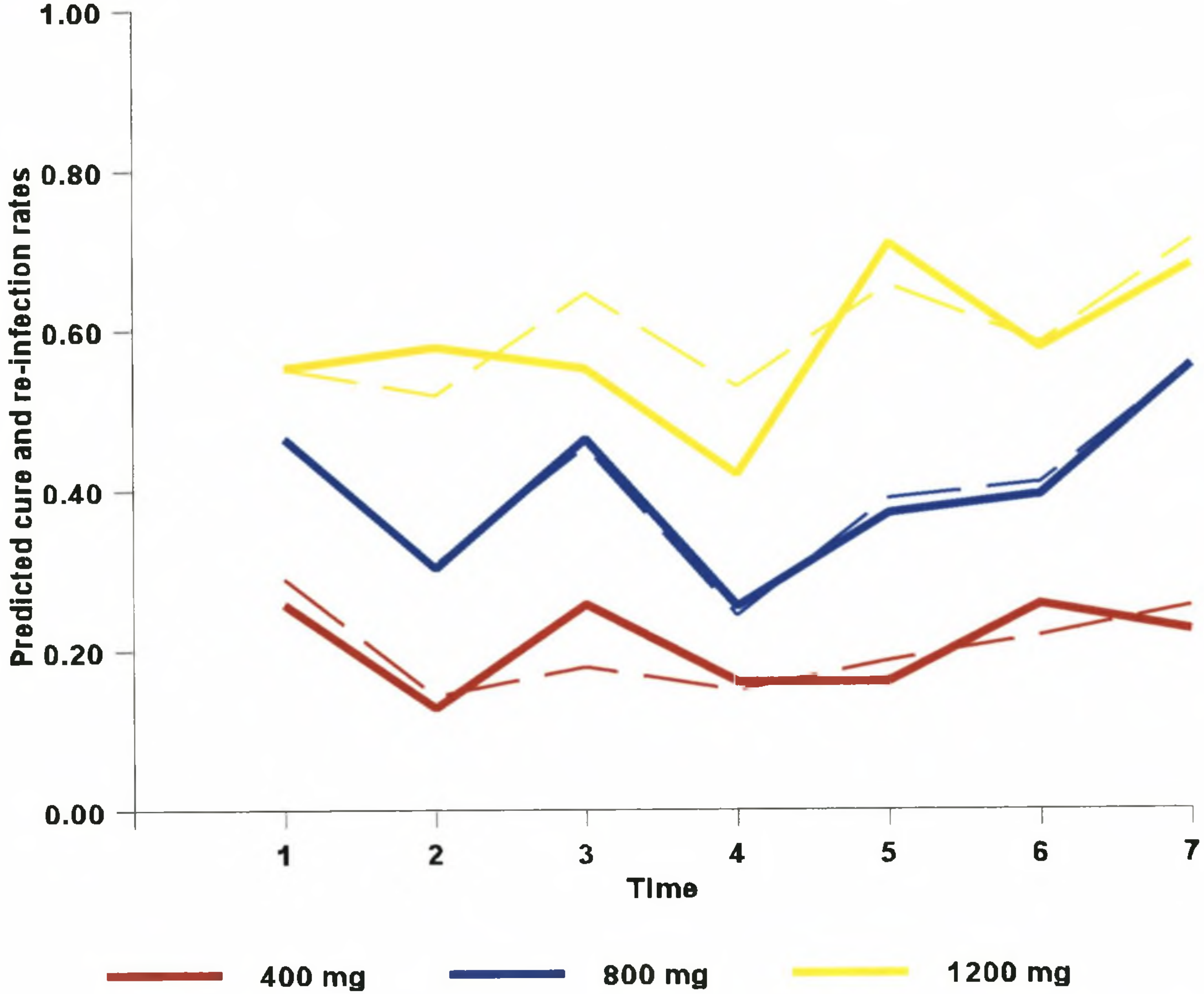

Fig. 18: Observed (solid lines) and predicted (dashed lines) values for alternating cure and reinfection rates. Results for the 800 mg dose match closely.

1 Seasonal effect on cure rate

Modelling over the non-treatment occasions detected a significant time (= seasonal) effect between the first two non-treatment occasions and the third. During the third occasion there was approximately 4% less reinfection ($p = 0.0029$). Treatment and non-treatment occasions are defined in relation to season, in Table 17. In the Western Cape, natural rainfall is in winter. However, vineyards are often irrigated with microjet systems. This may help to maintain a microclimate suitable for survival and development of the eggs in the soil, throughout the year.

Table 17: Treatment and non-treatment occasions in relation to season.

Date	Occasion	Season	Month
October 7 - 9, 1997	Treatment 1	Summer	0
October 10 - January 27, 1998	**Non-treatment 1**	Summer	1 - 4
January 28 - 30, 1998	Treatment 2	Summer	4
February 1 - May 27, 1998	**Non-treatment 2**	Autumn - Winter	5 - 8
May 27 - 29, 1998	Treatment 3	Winter	8
May 30 - Sept 16, 1998	**Non-treatment 3**	Winter - Spring	9 - 11½
Sept 17 -19, 1998	Treatment 4	Spring	11½
October 15, 1998	Final stool samples	Summer	12

Increased egg counts during the first two non-treatment occasions (Table 17), signify greater reinfection in summer/autumn, than in winter/spring. This is because the prepatent period for infection or reinfection by *Trichuris* to express as eggs in stools is between two and four months (Beaver *et al,* 1984; Horrii & Usuii, 1985; Schmidt & Roberts, 2000). This elapse of time is necessary for ingestion of eggs containing larvae, hatching, migration and development of larvae to adults in the intestinal mucosa, copulation by adults and egg production by females (Fig. 7). It has been suggested that seasonality of transmission of geohelminths may be an important factor to consider when planning a schedule for mass chemotherapy (Albonico *et al*, 1999; Bennett & Guyatt, 2000). The importance of monitoring a control group in any community-based intervention if rate of transmission can vary seasonally and from year to year, has also been emphasised (WHO, 1998a; Montresor *et al*, 1998; Montresor *et al*, 1999).

Late summer is harvest time in the vineyards around the school. Juice dripping from bunches of plump, ripe grapes, loaded onto trailers en route to the wineries, dampens the roads. Some kinds of grapes must be picked at night to control the sugar content, because that influences the character and flavour of the wine. In the vicinity of the wineries, the aroma of fermentation is characteristic. Most people are busy in the vineyards and there are school holidays. Several tasks in the culture of vines must be done meticulously by hand. Like pruning, training growth along trellises and picking the grapes. Within this scenario, nearly all the faecal samples analysed at the end of February 1998, approximately a month after the second treatment (Table 17, late summer) contained grape skins and pips. The children were questioned informally about this, and they revealed that during grape harvesting they eat grapes that fall to the ground. They also confirmed that the vineyards are often used as public toilets. It is too far for people working there to go to domestic toilets. Also, these are usually shared by several families and frequently consist of pit latrines. Pressure on primitive latrines and biophysical realities, mean that there is no practical alternative to defecation in the vineyards.

The school has flush toilets that are clean, as well as adequate facilities for washing hands. However, during a national census in 1996, enumerators recorded the toilet facilities in the homes in the community around the school. There were 10 enumerator areas within a 5 km radius of the school. The percentage of households with non-flush toilets in these areas ranged from 1 to 51%, with a mean of 19%. Further away, between 40 and 100% of households were recorded as <u>not</u> having flush toilets. During the course of the study, some children in the negative control group treated with placebo, who started with no worms, became infected (Fig. 17). The source of these new infections and all the reinfections in the treated groups, must have been mainly in the farm environment, rather than at the school.

2 Egg reduction rate (ERR)

This term (ERR) refers to reduction in mean egg count after deworming expressed as a percentage of the original counts before deworming (100%). ERR is probably a more important measure of efficacy than reduction of prevalence as indicated by CR. This is because ERR reflects the extent of reduction of contamination of the environment by the eggs that perpetuate infection. For instance, the current mass deworming programme on Pemba Island (Zanzibar, United Republic of Tanzania) is successful in terms of public and community health because it is clearly effective in terms of ERR. This is despite only small reductions in prevalence due to rapid reinfection during the initial years of the intervention (Albonico *et al*, 1997; Albonico *et al*, 1999; Montresor *et al*, 1999).

Montresor *et al* (1999) have described why the success of mass deworming programmes depends on many factors. They have emphasised the importance of monitoring representative groups of children in order to evaluate delivery by programmes and the effectiveness of anthelmintics used. Reduction of intensity of infection is particularly important, and reflects through reduction of mean egg counts and/or high ERR's. Monitoring of ERR in cohorts suitable for control purposes, is better than CR for initial screening of possible resistance to anthelmintics (WHO, 1998a; Bennet & Guyatt, 2000).

In this thesis, ERR is evaluated in terms of reduction of geometric mean egg counts. This is necessary because of the severely skewed negative binomial distribution of egg counts discussed previously (Anderson, 1986; Bundy *et al*, 1992). Derivation of the geometric mean for a series of egg counts is described in the list of definitions on page viii.

All the doses of albendazole were highly efficacious in that they maintained ERR's in excess of 96% (Tables 18 & 19; Fig. 19). When expressed in this way, i.e. relative to baseline egg counts, the ERR's for all the doses of albendazole exceed the benchmark for efficacy against *Trichuris* recommended by WHO, which is 50% (WHO, 1998a; Bennet & Guyatt, 2000) (Table 19).

The consistency of the results precludes any need for statistical analysis. ERR was proportional to dose of albendazole in that 1200 mg > 800 mg > 400 mg. The ERR's confirm efficacy of mass deworming with albendazole against *Trichuris* in terms of public and community health, under the epidemiological conditions pertaining at Rawsonville Primary School. Results for *Ascaris* are not directly relevant to this thesis, but all the doses of albendazole eliminated this worm completely and rapidly.

Table 18: Geometric mean counts of *Trichuris* eggs during a series of four treatments with albendazole, replicated at three doses.

Rx group	Baseline epg	n	After 1 Rx	After 2 Rx	After 3 Rx	After 4 Rx
400 mg	961	31	35.9	16.5	36.1	30.7
800 mg*	1015	43	12.0	4.5	11.8	6.5
1200 mg*	973	39	6.0	4.0	3.6	2.8
Negative control**	0	32	1.4	1.1	2.1	1.7

* Given as 400 mg on successive days

**The negative control group were treated with placebo

Table 19: Egg reduction rates (%) relative to *Trichuris* egg count before four treatments with albendazole, replicated at three doses.

Rx group	Baseline epg	n	After 1 Rx	After 2 Rx	After 3 Rx	After 4 Rx
400 mg	961	31	96.3	98.2	96.3	96.8
800 mg*	1015	43	98.8	99.5	98.8	99.3
1200 mg*	973	39	99.4	99.6	99.4	99.7

*Given as 400 mg on successive days

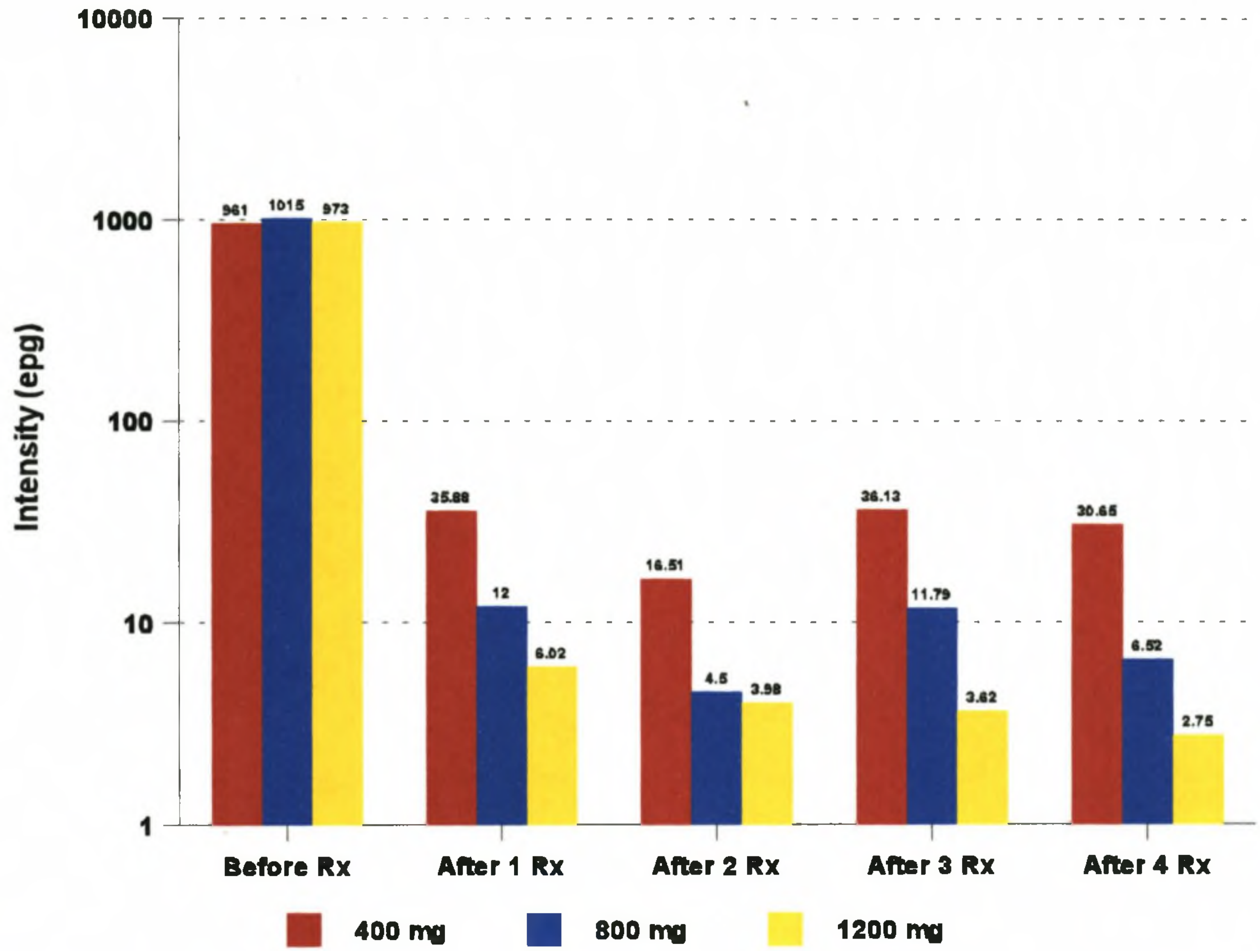

Fig. 19: Intensity of trichuriasis as reflected by egg counts (epg) expressed as geometric means, during the series of four albendazole treatments, at doses of 400, 800 and 1200 mg.

Another way of expressing ERR is shown in Table 20. Here ERR was calculated for GM egg counts before and after each treatment occasion, rather than by continuous referral to baseline GM egg count. Presentation in this way incorporates the continuous interaction between cure and reinfection. These ERR's do not always achieve the benchmark efficacy of 50% suggested by WHO, particularly when the dose was 400 mg (WHO, 1998a; Bennett & Guyatt, 2000). The results confirm the trend for CR's, i.e the doses of 800 and 1200 mg were more effective than the 400 mg dose.

Table 20: Egg reduction rates (%) calculated from residual geometric mean egg counts before and after each treatment.

Rx group	Baseline epg	n	After 1 Rx	After 2 Rx	After 3 Rx	After 4 Rx
400 mg	961	31	96.26	67.31	32.08	20.51
800 mg*	1015	43	98.82	37.50	58.62	61.11
1200 mg*	973	39	99.38	99.38	66.67	50.0
Negative control**	0	32	0	0	0	0

* Given as 400 mg on successive days

**The negative control group was treated with placebo

3 Possible resistance to albendazole

Some children were continuously infected by *Trichuris* during the series of treatments with albendazole, suggesting the possibility of resistance. The number that remained infected reduced in proportion to the dose (Table 21). The GM egg count before deworming of the constantly infected children was 1789 epg (range 323 - 16 800). This is substantially more than the GM of 803 epg (range 320 - 32 760) for children who were cured.

Table 21: Numbers of children who were continuously infected by *Trichuris* during treatment with albendazole.

Dose of albendazole	Number of children continuously infected
400 mg	15 (48%)
800 mg*	9 (21%)
1200 mg*	1 (2.5%)

*Given as 400 mg on successive days

No reports of genetic resistance to albendazole by any species of *Trichuris* were detected in the literature. In a direct communication in October, 2000, Andrew Bennett of the Welcome Centre for the Epidemiology of Infectious Diseases in Oxford, confirmed this. However, cases of persistent infection after treatment are well known in people and animals in zoos. These could be related to different metabolisms of the drug by the individual, or reduction of exposure to the drug due to chronically rapid intestinal transit time, or to a dietary component which binds drug and reduces the therapeutic availability. Another possibility is that persistent infections are from larvae that were in the crypts of Lieberkühn, or buried in the intestinal mucosa, so that they were sheltered from anthelmintic (Fig. 7; A2-A3).

To establish whether real genetic resistance exists, it would be necessary to detect resistance alleles by genotype screening assays (Bennett *et al*, 1999; Bennett & Guyatt, 2000). Preliminary procedures would require collection of eggs from the continuously infected children for testing in three ways. Firstly embryonated eggs should be exposed to pharmacological concentrations of albendazole to test for an ovicidal effect. Secondly, according to Prof Jack Chernin at the University of Portsmouth, *Trichuris* eggs can be cultured *in vitro* to hatch live larvae. Under controlled conditions, these larvae could be exposed to appropriate concentrations of albendazole to test for a larvacidal effect. Finally, embryonated eggs could be dosed to human volunteers (Horii & Usuii, 1985) or alternative animal hosts, who were not infected by *Trichuris*. After patent infection was established, the volunteers or animals would be treated with albendazole to test effectiveness. If these preliminary tests tended to confirm resistance, the genetic mechanism would have to be established by comparing the DNA sequences of resistant and susceptible worms.

There was a recent example of suspected resistance to praziquantel by *Schistosoma mansoni* in Senegal, after very low CR's were obtained (WHO, 1998b). However, when the treatments were repeated, results were good. Further study has elucidated two reasons for the low CR's. Initially, only CR was considered in communities where intensity of infection was high and reinfection rapid. In fact ERR's were good, despite the poor CR's (WHO, 1998b). Secondly praziquantel does not kill the immature schistosomes that can be a large component of parasite load when incidence is high. Survival of the immature stages created an impression that there was resistance because of treatment failure. However, when treatment was repeated within two to eight weeks, i.e. when previously immature schistosomes has progressed to adults, CR's were good (WHO, 1998b). The duration of the current series of treatments with albendazole should have precluded any possibility of a differential efficacy between adult and immature forms of the parasite, except for the possibility of larvae sheltered in the crypts of Lieberkühn and/or mucosa, mentioned earlier.

Drug quality control can be a factor in at least two ways. Firstly, the anthelmintic must conform to molecular purity specifications. Mebendazole polymorph A, as discussed in the section on CR's, is an example of active ingredient molecular quality failure. Despite this, it has been marketed (Charoenlarp *et al*, 1993). Secondly, the formulation in which the anthelmintic is available, such as tablets, suspension or solution, must deliver an effective dose of the right active ingredient. WHO have reported that a recurrent problem in developing countries is the circulation of generic drugs of substandard quality (WHO, 1998b). They estimate that 5-7% of the pharmaceutical world market may consist of counterfeit drugs.

4 Haematology

It is well established that elimination of intestinal parasites can improve the micronutrient status, behaviour, physical performance, growth, cognitive function and learning of children (Stephenson, 1980; Stephenson, 1989; Simeon *et al*, 1995; Hadji, 1999; Oberhelman, 1998; Forrester *et al*, 1998). The benefits will be enhanced when infection is prevented from soon after birth, because nutritional impairment often starts in infants (Birkin *et al*, 1998). By the time children reach primary school, their nutritional status and effects related to it, reflect a chronic situation. Sometimes maternal nutrition status and/or ingestion of toxins can result in low-birth-weight babies that can also be mentally retarded, and the compromise can be permanent (Binkin *et al*, 1988). For example, consumption of alcohol, hard drugs and smoking during pregnancy, can damage foetal development.

Haematological results are presented in terms of haemoglobin and eosinophilia (Tables 22 & 23).

4.1 Haemoglobin

Haemoglobin (Hb) in red blood cells can be a good reflection of iron nutrition (Kruger *et al*, 1996). A previous study in five primary schools in the same Health Region, of which Rawsonville was one, reported significant improvements in HB concentrations after deworming with albendazole (Kruger *et al*, 1996). There was an additive effect when deworming was combined with dietary iron supplementation.

Changes in Hb concentrations recorded during this study are summarised in Table 22. The standard deviations were larger than the increments in Hb concentration. Repeated measures analysis of variance was not able to differentiate a significant treatment effect from change due to time elapsed, which was similar for all the doses of albendazole.

On the basis of classification of anaemia as a Hb concentration of < 11g/dl, there were changes in prevalence after the series of treatments. In the group treated with 400 mg albendazole prevalence was 11% before deworming and 8% afterwards. In the 800 mg group prevalence of anaemia decreased from 10% to 7%, but in the 1200 mg group it increased from 15% to 17.5%. In the negative control group, prevalence of anaemia was 9% at the start of the study, but none of the children had a Hb level < 11g/dl at the end of the RCT.

Table 22: Arithmetic mean haemoglobin (Hb) concentrations and standard deviations (bracketed) before and after four treatments with albendazole or placebo (negative control).

Treatment	Mean Hb concentrations (g/dl)		
	Before Rx	After Rx	Change
400 mg albendazole	12.16 (0.80)	12.38 (0.90)	+0.22
800 mg albendazole*	11.77 (0.90)	12.03 (0.70)	+0.26
1200 mg albendazole*	11.76 (0.70)	12.22 (0.07)	+0.46
Negative control**	11.87 (0.70)	12.12 (0.07)	+0.25

*Given as 400 mg on successive days

**The negative control group was treated with placebo and were not infected by *Trichuris* at the start of the study.

The equivocal results for Hb and anaemia, may relate to several factors. Statistical power in terms of the number of children in each treatment group, may have been insufficient. Another could have been that the time span of one year was too short. However, a major confounding effect was probably the age of the children, in that if prevention of helminth infection was achieved from infancy, benefits should be more clearly defined. This is especially likely when one considers that when helminth infections are prevalent throughout a community, it indicates widespread contamination of the whole environment with human faeces. This inevitably indicates that children in the community are also exposed to an increased risk of diarrhoeal and dysenteric diseases caused by enteropathogenic protozoa, bacteria and viruses. The key roles in community and public health of a clean environment, and of clean food and water, are very real indeed.

4.2 Eosinophilia

Helminthic infection is the main cause of eosinophilia in developing countries (Weller, 1991; Pritchard *et al*, 1997; Rothenberg, 1998). It is well known in medical practice that anthelmintic treatment can reduce eosinophil count (Gilman *et al*, 1976; Bowie *et al*, 1978). However, there does not appear to be published information on results of mass deworming programmes in terms of effects on community-based eosinophilia. Part of the importance of peripheral eosinophilia is that an end product of humoral immune responses driven by T-helper 2 (Th2) lymphocytes and their cytokines (Weller, 1991; Rothenberg, 1998). Activated eosinophils are effector cells of this arm of the immune system. Therefore, reduction of eosinophil counts is some evidence of down regulation of humoral immune responses. These immunological relationships are the basis for a major hypothesis that helminthic infestation might increase susceptibility to infection by the human immunodeficiency virus and mycobacteria (Bentwich *et al*, 1996; Bentwich *et al*, 1997; Adams *et al*, 1999; Bentwich *et al*, 1999; Fincham & Markus, 1999).

Repeated measures analysis of variance confirmed significant reductions in arithmetic mean eosinophil counts, and in the prevalence of eosinophilia, after deworming with albendazole in the current study.

In the negative control group treated with placebo, in which the children had no worms initially, trends were opposite to those after albendazole treatment, possibly because some children became infected. All results pertaining to eosinophilia are summarised in Table 23. Counts of other white blood cells did not change during the albendazole treatments, and there was no seasonal effect suggestive of atopic influence.

Table 23: Changes in mean eosinophil counts and percentages of children with counts exceeding the normal paediatric range.

	Before deworming		After 2 dewormings[a]		After 4 dewormings[a]	
Treatment and number of children	Means (SEM)[b]	% > 0.45[c]	Means (SEM)[b]	% > 0.45[c]	Means (SEM)[b]	% > 0.45[c]
400 mg[d] (n = 37)	0.676 (0.087)	51	0.382 (0.035)	35	0.397 (0.037)	35
800 mg[d] (n = 41)	0.762 (0.080)	66	0.548 (0.063)	49	0.462 (0.038)	41
1200 mg[d] (n = 40)	0.643 (0.075)	50	0.401 (0.071)	33	0.459 (0.061)	38
Negative control[e] (n = 37)	0.384 (0.037)	29	0.342 (0.031)	27	0.472 (0.046)	49

[a] After 2 and 4 dewormings, eosinophil counts were significantly reduced for all the doses of albendazole, with respective P values of <0.0001 and < 0.0353.

[b] SEM = standard error of the mean.

[c] Prevalence of eosinophilia. 0.05 - 0.45 x 10^9/l is the normal paediatric range.

[d] Albendazole *per os*, as *Zentel*® 400 mg tablets, SmithKline Beecham: Treatment intervals approximately 4 months, compliance observed dosed as 400 mg/day.

[e] Children in this negative control group were treated with placebo only. They had no worms when the study commenced, but infections developed progressively, which probably explains the increased eosinophil counts.

A mass deworming programme at another school has confirmed significant reduction of eosinophilia during deworming with mebendazole, with no change in other white blood cell counts, or any seasonal effect indicative of a possible atopic influence (unpublished data). There are approximately 300 pupils at the school, and all of them were dewormed at intervals of four months.

5 Anthropometry

The heights and weights of almost 500 children in the baseline survey was a substantial measure of the growth status of the children attending the school when expressed in terms of stunting, underweight and wasting (WHO, 1995). Hard data of this nature is needed by those responsible for child health and nutrition in South Africa. Results are reported in this context, rather than in relation to the anthelmintic study, because growth deficits are likely to reflect back to a very early age, possibly even to low birth weight (Binkin, 1988; WHO, 1995). It is generally known that alcoholism is a problem where the main industry is wine production, and the foetal alcohol syndrome is prevalent in the indigenous population. The prevailing human ecology is such that the growth status of groups of children in primary school, ranging in age from six to 16 years (mean 9), is not likely to show any statistically interpretable change due to anthelmintic treatments during the short period of one year. For example, some parametric statistical tests register significance when the mean of a variable changes by more than two standard deviations, after treatment. However, anthelmintic treatment could be beneficial in terms of learning at school and physical performance, which were not measured in this study. Those children who were severely infected, as shown by egg counts in Table 7, probably could benefit in terms of compensatory growth.

Nevertheless, deworming has been reported to have positive effects on growth of children infected by *Trichuris* and other helminths, in several other studies (Stephenson, 1980 & 1989; Callender, 1994; Simeon *et al*, 1995; Hadji, 1998; Oberhelman, 1998; Forrester *et al*, 1998). The study by Forrester (1998) also reported that high doses of albendazole, such as 1200 mg or more, may have an adverse effect on growth, due to suspected toxicity.

The anthropometric results from the baseline survey are summarised in Table 24. The prevalences of stunting and underweight in this population is cause for real concern and should receive attention. However, this is beyond the scope of this thesis.

Table 24: Percentages and frequencies of underweight, stunting and wasting in the baseline sample of children at Rawsonville Primary School. Based on international reference values (WHO, 1995)[1]

		Percent	Frequency
Stunting	**z-score < -2**	31.2	149/478[2]
	Percentile <3	36.4	174/478[2]
Underweight	**z-score < -2**	21	104/496[2]
	Percentile <3	26	129/496[2]
Wasting	**z-score < -2**	3.1	11/351[2]
	Percentile <3	4.6	16/351[2]

[1]Age in months: mean 114; range 75.4 - 194.8; median 112.8

[2] Numbers changed due to flagging of unacceptable ages by the software.

Although changes in height and weight of the children in the treated groups were not statistically different, what appear to be consistent trends are summarised in Table 25.

Table 25: Changes in height and weight during treatment with albendazole or placebo.

Treatment	Changes in height (cm)	Changes in weight (kg)*
Albendazole 400 mg	+2.25	+1.83
Albendazole 800 mg	+2.70	+1.79
Albendazole 1200 mg	+2.20	+1.80
Placebo	+0.70	+0.50

*The changes were obtained by subtracting the arithmetic mean group weight before deworming started from the mean immediately after the final treatment.

It should be noted that while increases in height are real, changes in body mass may be artefacts. This is because variation in measurement of height should only arise due to reading error when the method is standardised, as in this study, because young people can only increase in height. However, body mass (weight) varies physiologically and pathologically, as well as due to reading error. Thus, there can be acute changes of mass due to dehydration, vomiting, diarrhoea, eating, starvation and drinking.

6 Hypothetical toxicity of albendazole

The growth results specified in the foregoing Table 25, do not support the hypothesis by Forrester *et al* (1999) that albendazole may impair growth of children due to toxicity, when the dose is 1200 mg or more. Moreover, albendazole has been used at very high doses that were repeated many times, in patients with AIDS or hydatid disease, and toxicity has not been a problem (Kelly *et al*, 1996; Mohamed *et al*, 1998). The doses used in hydatid disease are massive.

7 Prospects for mass deworming in South Africa

The results of this trial show that a sustained deworming programme can reduce the return of worm eggs to the environment enormously, even when sanitation is inadequate. School-based health and nutrition programmes in Ghana, Tanzania, India and Indonesia have shown that the educational sector is capable of delivering anthelmintics to school children. Theory and practice indicate that targeting treatment at school children reduces infection levels in the community as a whole (Bundy *et al*, 1990; WHO, 1996). The fact that children assemble daily in one place, the school, provides an opportunity to deliver mass treatments through an existing infrastructure (Bundy & de Silva, 1999). In South Africa, this practice has only recently been introduced, when teachers dewormed children at Langebaan Primary School on the West Coast (author's unpublished data). Teachers at Rawsonville Primary School also dewormed the children during this study and the whole school at the end of the study. In Khayelitsha, teachers at 12 schools are implementing a deworming programme. In fact deworming by teachers is the only way to implement mass deworming. However in the KwaZulu Natal Province of South Africa, teachers have refused to deworm the children they teach.

CHAPTER 5

Conclusions and Recommendations

1) The RCT demonstrated that the 400 mg *stat* dose of albendazole advised internationally for use in mass deworming programmes (WHO, 1998; Bennett & Guyatt, 2000) was inferior in terms of CR, under the epidemiological conditions pertaining in the Western Cape Province of South Africa. ERR was also less than the benchmark of 50% (WHO, 1998; Bennett & Guyatt, 2000), when ERR was calculated on residual egg counts at the third and fourth treatments (Table 20). Therefore, it is recommended that a dose of 800 mg given as 400mg/day on successive days should be used under local conditions, since the efficacy thereof was similar to the 1200 mg dose, the cost would be less and compliance would be better.

2) A key aspect of this thesis is to explain how simple and relatively inexpensive technology can be used to monitor helminthiasis as an indicator or index of child, community and public health. A high prevalence of trichuriasis confirms that the ecology is degraded in the sense that the communal environment is polluted by human faeces. The health indications are fundamental, as well as direct and indirect. There are implications of overcrowding, lack of sanitation and contamination of food and water. The risk of diseases caused by a wide spectrum of enteropathogenic protozoa, bacteria and viruses is enhanced. The current outbreak of cholera is a good example. It started in KwaZulu-Natal and has spread to Gauteng, Mpumalanga, Swaziland, Zimbabwe and Mozambique. Tens of thousands of people have been infected and many have died. The need to use a practical, cost effective method to define, track and to help to rectify these adverse human situations is clear.

3) There are several South African communities who were probably never aware that public health and prevention of disease depend primarily on application of a few basic principles. These include knowledge of how to avoid exposure to infection through personal behaviour and habits, hygiene, sanitation, clean water and food, and proper housing. The circumstances usually relate to poverty and are beyond the control of the affected communities. Farm labourers are often in this situation, as are people living in urbanised informal settlements.

4) It is recommended that labourers working in vineyards or orchards should be provided with portable toilets and this process should be participatory to ensure that the workers accept and use the toilets. To achieve this, they need to be informed about why use of such facilities will be beneficial to health, and about efficient operation of sanitation and toilets. The number of people per toilet should not exceed 30. The toilets must be mounted on wheels so that they can be moved around easily. The type of chemical toilet used by construction workers and municipal employees may be suitable, provided that the chemical effluent from these toilets does not itself cause a pollution problem.

5) The literature confirms that South Africa is behind many other developing countries in the implementation of international recommendations with regard to monitoring and control of helminthiasis, and related diseases. The possibility that chronic, hyperendemic helminthiasis is enhancing the epidemics of HIV and tuberculosis must be noted and research should be undertaken locally.

6) The literature and medical practice also confirm that effective anthelmintic treatment can be of immediate benefit to the infected individual, and especially to children, in terms of minimising morbidity and preventing medical and surgical complications.

7) Mass deworming programmes that treat nearly all school-age children simultaneously and regularly, can have massive effects in terms of child and community health. It is these children who carry most of the trichuriasis, ascariasis and hookworm infestation in communities. The benzimidazole anthelmintics are ovicidal and larvicidal. Therefore these programmes can reduce the load of infective eggs in the environment, and in this way slow the incidence of infection.

8) To achieve benefits enumerated in the two preceding points, anthelmintics must be effective. It is necessary to monitor efficacy constantly by methods similar to those described in this thesis. The persistently infected individuals in all the groups treated with albendazole show that the possibility of real genetic resistance to albendazole was not excluded by the current results. Veterinary experience warns us that helminths can develop resistance to anthelmintics, although the conditions of exposure are different.

9) The real solution to prevention of hyperendemic helminthiasis, and related diseases, does not lie in medication. Non-medical prevention can be achieved by environmental and human development. They need to know how the infections cycle, and how to avoid exposure. People need proper houses within which the occupational density is not too high. Clean water and effective sanitation are key factors, as are domestic, food and personal hygiene. There are local examples in Cape Town of how implementation of some of these preventative measures has drastically reduced the prevalence of worms, compared to high prevalence in adjacent communities. Mass media, including national television should be used to spread the message.

10) Finally, the human population of South Africa is undergoing dynamic changes. Key factors driving these are poverty, urbanisation, migration and disease. It is in this context that the results now reported and discussed are very relevant. If disease and poverty impair the vigour of the

nation, we may not be able to compete internationally.

APPENDIX 1

INFORMED CONSENT FOR MINORS

1) I, ____ (PRINT NAME IN FULL), am the legal parent or guardian of the minors listed in the table below.

Names of Minors	Date of Birth	Permanent Numeric Code
1		
2		
3		
4		

2) I have been fully informed of the purpose and nature of the study and the procedures, as explained on the reverse side of this form and I understand what it says.
3) All routine procedures and medical examinations will be carried out by dietitians, medical technologists, medical scientists, doctors, nursing staff and teachers, as appropriate.
4) I understand that I can recall my consent on behalf of the child, or children, mentioned above at any time without prejudicing either myself or him/her with regard to receiving routine medical care.
5) All information will be treated as confidential.

Name of Guardian :________________________________ **Code number**_________

Postal Address : ____

Telephone Number __________________________ **(H)**______________________**(W)**

SIGNED AT RAWSONVILLE THIS...........DAY OF................................, 19.........

Guardian..

Person who informed guardian..

As Witness...

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