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REPORT OF THE
WHO INFORMAL CONSULTATION ON THE
USE OF CHEMOTHERAPY FOR THE CONTROL OF MORBIDITY
DUE TO SOIL-TRANSMITTED NEMATODES IN HUMANS

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Schistosomiasis and Intestinal Parasites Unit
Division of Control of Tropical Diseases

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1. Opening Ceremony

Ladies and gentlemen, friends and colleagues, it is my pleasure to welcome you to this **Informal Consultation on the Use of Chemotherapy for the Control of Morbidity Due to Soil-transmitted Nematodes**.

Large-scale chemotherapy plays a central role in the control of many parasitic infections such as lymphatic filariasis, onchocerciasis, schistosomiasis and intestinal nematode infections. The impact of chemotherapy on these infections varies. The lymphatic filariasis experience has shown that chemotherapy is an effective tool for transmission control. Chemotherapy for soil-transmitted nematodes represents an effective tool for the control of mortality and morbidity. Regular chemotherapy of infected populations reduces mortality and morbidity in pre-school children, improves nutritional status and school performance of school children, and improves the health and well being of pregnant women.

In 1990, a WHO Informal Consultation on Intestinal Helminth Infections held in Geneva, stressed how chemotherapy could reverse the effects of infections in children. In 1994 another WHO Informal Consultation addressed the control of hookworm infection in girls and women. This Consultation recommended that in areas where hookworm infections are endemic, and where anaemia is prevalent, hookworm control using anthelmintic treatment should be included in strategies designed to improve the health, development and nutritional status of girls and women.

In Zanzibar, chemotherapy-based control of soil-transmitted helminths, with a single dose of generic mebendazole has been found recently to improve the nutritional status of school-age children in spite of intense transmission, reinfection and incomplete deworming. We will hear reports of these results during this Consultation. Similar promising results have been achieved with other single-dose anthelmintics such as albendazole, levamisole and pyrantel. These four drugs are now included in the recently revised Essential Drug List of WHO as the drugs to be used against soil-transmitted nematodes.

All this recently gained information seems to suggest that it is not the relative efficacy of each drug that is the key to success, but with drugs that are similarly efficacious to control morbidity, it is the low cost of the intervention. Cost of anthelmintics and cost of drug delivery play an essential role in the long term sustainability of control programmes.

There are alternative options to drug delivery of which the school system is presently one of the more promising. Integration of large-scale treatment at the primary health care level may be another alternative. We will also hear about the successful experience of integrated family planning and parasite control projects promoted by the Japanese non-governmental Organization [JOICFP] and the Semana Nacional de Salud in Mexico.

This Informal Consultation is also an attempt to address other questions about the use of chemotherapy and its long-term effects that have not yet been thoroughly discussed in a WHO forum. There is still no consensus on how frequently and when infected communities should be treated to achieve the best results in terms of reduction of morbidity and possible impact on transmission. We will hear about past and present experiences in this area from large-scale control programmes in several endemic countries.

Drug resistance in intestinal nematode infections of ruminants is a major threat to morbidity control in animals. You will discuss what lessons are to be learned from the experience of the veterinarians and what should be recommended as appropriate measures to be taken to prevent the development and spread of drug resistance against human anthelmintics.

Thank you for sharing your time and expertise with us. We look forward to receiving your advice and recommendations.

Dr R.H. Henderson
Assistant Director-General

2. Purpose of the Consultation

Since the Informal Consultation on Intestinal Helminths held in Geneva (WHO/CDS/IPI/90.1) several major projects have improved prospects of introducing effective programmes for controlling morbidity due to soil-transmitted nematode infections based on the regular treatment of populations in endemic areas with anthelmintic drugs developed by the research-based pharmaceutical industry. Pilot studies and operational research have not only shown reductions in the intensity of infections but also that chronic morbidity, expressed as impaired growth, poor cognitive performance and iron-deficiency anaemia, is significantly reduced after treatment.

Ministries of Health and Education have established school health programmes in a number of countries with the help of the Partnership for Child Development. These national Partnership programmes have now delivered albendazole and praziquantel on two occasions to 85 000 children in first cycle schools in Ghana and to 110 000 Primary School children in Tanzania. In Central Java in Indonesia 55 000 Primary School children have received albendazole while the Mid-day Meals Commission in Gujarat in India has delivered albendazole, vitamin A and iron supplements to about 3 000 000 children. New health education materials which deal with issues related to worm infections, hygiene and nutrition have been developed for the programmes in Ghana, Tanzania and Indonesia and are now being used by trained teachers in between 250 and 600 Primary Schools in each country. Partnership programmes are also being developed in Viet Nam and Colombia.

The main aims of any control programme should be concerned with reducing the intensity of infection and then sustaining the reduction at levels below those associated with morbidity. The nematode infections of major interest are those caused by *Ascaris lumbricoides*, *Ancylostoma duodenale*, *Necator americanus*, and *Trichuris trichiura*. These nematodes are widespread, highly prevalent and extremely persistent (Savioli, et al.). Their life histories, population biology and related pathologies are well known (Crompton et al., 1985, 1989; Bundy and Cooper, 1989; Pawlowski et al., 1991). It is also important to consider *Strongyloides stercoralis*, another nematode which also invades the human gastrointestinal tract, but has a different life history from the other common soil-transmitted nematodes (Grove, 1989). All these nematodes

thrive where poverty, malnutrition, inadequate sanitation, lack of clean drinking water and minimal health care prevail.

The purpose of this Consultation was to discuss how to optimise the delivery and use of anthelmintic chemotherapy in the community. Specific questions addressed included: how should a base-line epidemiological survey be carried out?; is it realistic to undertake screening during a control programme?; can groups at risk of morbidity be identified?; can anthelmintic drugs be used in combination where soil-transmitted nematodes, filarial nematodes and schistosomes occur together?; is there a risk of inducing drug resistance?; how can community compliance be secured?; how can progress be sustained? Most importantly, since any control measures are likely to be constrained by the capacity of needy communities to plan, manage and implement programmes against a background of meagre resources, the Consultation considered how the control of soil-transmitted might be integrated more cost-effectively into other health care programmes.

3. Essential Epidemiology

A programme to control morbidity due to soil-transmitted nematodes should always begin with a survey of infections. This is best performed by the microscopical examination of faecal samples collected from a random sample of people selected from the group of interest within the community. Because school-age children often tend to harbour the heaviest infections they can be used to assess whether soil-transmitted nematodes threaten the health of school-age children and the community at large.

The recommended method for examining stool samples is the Kato-Katz cellophane quantitative thick smear technique described by Ash *et al.* (1994) in *Bench Aids for the Diagnosis of Intestinal Parasites*. This method enables intensity of infection to be measured indirectly and expressed as number of eggs per gram of faeces (epg) as egg counts. Any sample containing even a single egg contributes to the estimate of prevalence. Each species of worm should be identified, although the eggs of the two common hookworm species cannot be distinguished and should be reported simply as hookworm. The number of eggs seen of each species should be counted so that the intensity of infection can be estimated. The presence of the larvae of *S. stercoralis* should be noted.

However, the Kato-Katz technique is not appropriate for the detection of *S. stercoralis* larvae.

The easiest estimate to make of intensity of infection is the arithmetic mean of the concentration of eggs in faeces (epg) calculated for each species using as denominator the total number of subjects studied or the total number judged to be infected. It should be clearly stated as to which denominator has been used. Because *S. stercoralis* multiplies within the host it is unclear whether the concentration of larvae has any value to assess morbidity.

The impact of programmes is best expressed as the percentage fall in arithmetic mean egg per gram (epg) counts. If the data on epg before and after treatment have been collected for different samples of individuals then the means should be calculated separately for each group and the difference between the two means should be expressed as a percentage of the mean epg count before treatment.

$$X = \frac{(\text{Mean epg before treatment} - \text{Mean epg after treatment}) \times 100}{\text{Mean epg before treatment}}$$

data on egg counts for the same individuals are available before and after treatment (paired data) then the difference in epg should be calculated for each individual and the mean of these differences should be determined. Changes in mean egg counts can be expressed as a percentage of the mean egg count before treatment.

$$X = \frac{\sum_{i=1}^n (\text{epg before treatment})_i - (\text{epg after treatment})_i}{n} \times 100$$

4. Review of available anthelmintic drugs (Tables 4.1 and 4.2)

Several well evaluated anthelmintic drugs have been developed by the research-based pharmaceutical industry for the treatment and control of soil-transmitted nematodes and filarial nematodes. The drugs of interest in this Consultation are albendazole, levamisole, mebendazole and pyrantel (Table 4.1 and 4.2) together with ivermectin which is not included in the list of drugs

recommended by WHO for treatment of intestinal nematodes. Each of these drugs is recommended by WHO (WHO 1995) and in large-scale control programmes drugs should be used according to WHO recommendations. They should be of guaranteed quality and delivered according to the prescribing information produced by the manufacturers and approved in the country where administered. When anthelmintic drugs are used, it has become normal practice to evaluate efficacy in terms of either the “cure rate” (CR) or the “egg reduction rate” (ERR). These variables are defined and discussed in the explanatory notes to Table 4.1

4.1 Albendazole

Pharmaceutical form: Chewable tablets, 200 mg and 400 mg.

Dose: 400 mg single administration.

Category: benzimidazole derivative. Introduced in Australia in 1977 for the treatment of sheep helminths, and first approved for human use in 1982.

Mode of action: the drug binds to nematode tubulin preventing the formation of microtubules and so stopping cell division. One consequence is impairment of nutrient uptake by the parasite. Albendazole also has larvicidal and ovicidal effects.

Pharmacokinetics: the drug is poorly absorbed and operates its anthelmintic action directly on the gastrointestinal tract. It is rapidly and extensively metabolized by the liver and the sulfoxide metabolite is found in plasma when given at a higher dosage than 400 mg. The plasma concentration of albendazole is 15-49 times higher than that of mebendazole. The absorbed fraction is largely excreted in the bile and to some extent in the urine as the sulphoxide.

Efficacy: about 80 trials have been published on the treatment of intestinal helminths. As a single dose it is very effective against *A. lumbricoides* with cure rates (CR) and reduction in egg counts (ERR) between 85%-100%. The drug is effective against the hookworms (CR 57%-100% and ERR 73%-100%) and has been shown to be more active than other anthelmintic against *N. americanus*. It is less effective against *T. trichiura* with a CR between 10% and 67% and a ERR between 73% and 87% in comparative trials with mebendazole. For the treatment of *S. stercoralis* infection, a course of 400 mg for three days was reported in small studies with a CR between 50 and 67%. A recent study in Zanzibar has shown a CR of 43% of 400 mg daily for three consecutive days.

Safety: In 35 trials (13,013 patients) no side effects were reported. In 30 trials (9,220 patients) adverse effects affected 409 patients and were mild and transient. In a further 15 trials adverse effects were not sought. A few cases reported migration of *A. lumbricoides* through the mouth, occasional

gastrointestinal symptoms (epigastric pain 0.3%, diarrhoea 0.3%, nausea 0.2%, vomiting 0.1%), CNS symptoms (headache 0.2%, dizziness 0.1%), rare allergic phenomena (oedema 0.7/1000, rashes 0.2/1000, urticaria 0.1/1000). All were transient and disappeared after 48 hours. Liver function abnormalities and leucopenia have been reported occasionally, but only at higher dosages and after prolonged treatment. Albendazole has been shown to be teratogenic in rats and rabbits at high dosage. There were no reports of malformations following inadvertant exposure to high multiple doses to 15 cases during the first trimester of pregnancy, but albendazole should not be administered in the first trimester.

4.2 Ivermectin

Pharmaceutical form: chewable, scored tablet, 6 mg

Dose: 200µg/kg body weight single administration

Category: macro-cyclic lactone

Mode of action: the drug causes the paralysis in many nematodes and arthropods through the influx of chloride ions across cell membranes.

Pharmacokinetics: the drug is absorbed into the blood following oral administration and peak levels are reached 4h after oral administration. It is excreted almost entirely in the faeces.

Efficacy: few trials investigated the use of ivermectin for the treatment of intestinal helminths. Despite its multitude of uses in veterinary medicine and its activity against various life-cycle stages of many nematodes, in human medicine, its use has been almost exclusively as a microfilaricide for the treatment of onchocerciasis. It is currently licensed in France for the treatment of *Strongyloides stercoralis*.

The drug has been reported to be 100% effective against *A. lumbricoides* at dosages of 50-200 µg/kg (4 trials), 82-95% effective against *S. stercoralis* in single or two administration of more than 150 µg/kg (4 trials). 11-100% effective on *T. trichiura* according to the different dosage used (from 200 µg/kg single dose to 400 µg/kg in two divided doses with administration over 2 days) and 0-20% effective on hookworms.

Safety: mild adverse reactions (e.g. borborygmus, diarrhoea, constipation) have been reported in a small minority of patients. Ivermectin should not be administered during pregnancy.

4.3 Levamisole

Pharmaceutical form: chewable tablet 40 mg

Dose: 2.5 mg/kg single administration.

Category: a laevorotatory isomer of tetramisole. Marketed as veterinary anthelmintic in Belgium in 1965 and first introduced as an anthelmintic for human use in Brazil in 1966.

Mode of action: binds to the acetylcholine receptors of nematodes causing a spastic paralysis followed by the passive elimination of the worms.

Pharmacokinetics: levamisole is highly soluble in water and is rapidly absorbed almost completely by the gastrointestinal tract. Plasma peak levels are reached within 2 h of administration. The drug is metabolized in the liver and eliminated in the urine largely as metabolites within 2 days.

Efficacy: There are more than 60 clinical trials showing a high efficacy of levamisole against *A. lumbricoides* and hookworm infections. CRs of 86-100% and ERRs of 96-98% with a single dose have been reported for *A. lumbricoides* infection. For hookworm infection, CRs are in the range of 66%-100% and ERRs of 86-99% have been reported. In case of severe hookworm infections (*N. americanus*) a second standard dose may be given 7 days after the first treatment. The drug has a more variable effect against *T. trichiura* (CR 16-18%, ERR 73%). Repeated treatment with levamisole over a period of two years has been suggested to delay re-infection in African schoolchildren (Jancloes, 1989).

Safety: occasional vomiting (5%), dizziness (3%), headache (3%), weakness (2%), which are mild and transient. No laboratory abnormalities are detected at single dose of 2.5 mg/kg. The drug has shown no teratogenic effect at doses up

to 40 mg/kg in rats and in farm animals (Janssen Research Foundation, 1991). It may be safer than the benzimidazoles for use in pregnant women although no drug should be administered during the first trimester.

4.4 Mebendazole

Pharmaceutical Form: Chewable tablets of 100 and 500 mg.

Dose: 500 mg single administration or 100 mg twice daily for three days. The 500 mg preparation was initially introduced to be used with high dosages (up to 50 mg/kg) for the treatment of tissue nematodes and cestodes (hydatidosis, filariasis in association with levamisole, and trichinellosis).

Category: benzimidazole derivative. Introduced in 1972 for the treatment of intestinal nematode infections.

Mode of action: binds to nematode tubulin preventing the formation of microtubules and inhibiting cell division. It may also have larvicidal and ovicidal effects.

Pharmacokinetics: Almost insoluble in water, in humans is poorly absorbed by the gastrointestinal tract. The portion which is absorbed is rapidly metabolized by the liver and excreted in the bile. Plasma concentrations of mebendazole are detectable only with high dosages (1.5 g). The drug is largely excreted unchanged through the faeces.

Efficacy: Reports indicate a wide range of efficacy of mebendazole, perhaps due to differences in study design, possible geographical differences, different age groups enrolled, difference in infections treated, and so on. In comparative trials with albendazole, the efficacy of the single dose is similar for the treatment of *A. lumbricoides* (CR 98-100%, ERR 99-100%) and of *T. trichiura* (CR 14-70%, ERR 80-89%). It is less effective against the hookworms (CR 22-30%, ERR 70-82%).

Safety: a few cases have been reported of erratic migration of *A. lumbricoides*, mild gastrointestinal disturbance and transient abdominal pain and diarrhoea. Only high doses (50 mg/kg for 3-4 weeks) may give rise to severe abdominal pain,

raised transaminase levels, allergic conditions, CNS symptoms (vertigo, headache) (Davis, et al., 1986). Mebendazole has been shown experimentally to have teratogenic potential in rats at doses of 10 mg/kg body weight. A survey in pregnant women who inadvertently took mebendazole in the first trimester has not shown spontaneous abortion or malformations greater than those of the general population (FDA pregnancy category, USP D1, 12th edition, vol 1b, 1992). However, no drug should be administered during the first trimester.

4.5 Pyrantel

Pharmaceutical form: Chewable tablet 250 mg (as embonate).

Dose: 10 mg/kg, single administration.

Category: pyrimidine derivative. The drug was developed in 1966 with the first clinical trials in humans being conducted in 1968.

Mode of action: binds to the acetylcholine receptors of nematodes causing a spastic paralysis followed by passive elimination.

Pharmacokinetics: Insoluble in water, it is poorly absorbed in the gastrointestinal tract. Partially and rapidly metabolized in the liver, a small percentage is excreted with the urine and a large amount is eliminated unchanged in faeces.

Efficacy: In more than 40 trials, single dose of 10 mg/kg has shown to be effective against *A. lumbricoides* (CR 81-100%, ERR 82-100%). A single dose of 5 mg/kg has also proved to be effective against *A. lumbricoides* giving a CR of about 97% (Kobayashi et al., 1970). The drug is also effective against hookworms (CR 37-88% ERR 64-90%). It has shown to be more effective against *A. duodenale* (ERR 85%) than against *N. americanus* where repeated doses are needed especially to cure heavy infections.(ERR 71%).

Safety: In a study on 1,506 individuals, side effects were mild and transient including occasional diarrhoea (4.3%), abdominal pain (4%), nausea (3.5%), vomiting (2%), headache (3%), (Pitts 1974). Transient raised serum transaminase was detected in 2% of patients. Tests in rats, sheep and rabbits

have shown no teratogenic effects, but as with other drugs pyrantel should not be administered during the first trimester of pregnancy.

4.6 Rationale for the Choice of Drugs (Tables 4.1 and 4.2)

Drugs selected for a control programme should satisfy the needs of the majority of the population and must always be available in adequate amounts, in the appropriate dosage and packaging forms, on time and in the right place. Choice of drug depends on its i) safety record, ii) therapeutic effect, iii) cure rate or efficacy, iv) spectrum of activity, v) experience of local health professionals, vi) training of staff, vii) demographic factors and viii) financial considerations. The subject is reviewed by WHO in the current edition of *The Use of Essential Drugs* (TRS 850, WHO 1995). Only drugs included in this list should be chosen for any parasite control programme and should be approved or registered by the authorities for use in the programme.

4.6.1 Quality

Drugs must be manufactured according to good manufacturing practice and be of sufficient quality to perform as required. It is known that many counterfeit products exist (WHO/IFPMA, 1992) and may be utilised in control programmes. Counterfeiting of pharmaceuticals is a serious criminal offence and the handling of such products endangers human health. Counterfeiting costs the legitimate pharmaceutical industry about 5% of its share of world trades (WHO/IFPMA, 1992) amounting to about US\$19 billion in last sales (IMSS, 1995). However, it must also be recognized that the pharmaceutical performance of apparently identical products (generics) may be variable. These may vary substantially from the originator product, on which all technical data are based. It is necessary first to demonstrate that a product is not counterfeit or substandard and actually contains the stated compound. The German Pharma Health Fund has produced a simple thin layer chromatographic method for the identification of impurities and active ingredients in essential drugs including albendazole and mebendazole (Packaly *et al* 1994). It is also important to know how the product behaves with regard to features such as weight of active compounds and excipients used, disintegration and dissolution tests using standard pharmacopoeal methods in comparison to the originator. In the absence of reasonable similarity, the only approach would be a demonstration of efficacy *in vivo* (Albonico *et al.*, 1994).

Within this context a careful balance between quality of product and cost must be made, and contracts to purchase should be dependent on demonstration of adequate quality. Without this certainty, apparent savings may become considerable expenses and control programmes may be put in jeopardy or may even fail.

4.6.2 Costs

In view of the problems of ensuring satisfactory quality, it should be noted that the cheapest drug is not necessarily the most effective or the safest. When cost comparisons between drugs are made before purchase, the cost of the total treatment, including such factors as storage, delivery to site, treatment on site and monitoring, should be estimated and not only the unit cost of the drug itself (TRS 850, WHO 1995). Cost analysis is a complex but essential part of planning and an example of how to proceed for a large-scale control programme has been developed by Guyatt *et al.*, (1993). Cost effectiveness is another aspect of drug choice that should not be ignored at the planning stage, particularly if data from pilot studies in the region of interest are available. An example of a reasonably simple approach is this type of analysis proposed by Holland *et al.* (1996) working in rural Nigeria.

5. Examples of the Control of Soil-transmitted Nematodes using Chemotherapy

Control programmes aimed at reducing morbidity due to infection with soil-transmitted nematodes have been carried out in a variety of countries with widely diverse terrain, climate, demography and cultures. Some experience is common to each programme, but planners should be careful to identify factors that are important in their local context.

5.1 Self-sustained programmes in Japan

Israel, Japan and South Korea have achieved successful and sustained control of intestinal nematode infections. Japan has led the way in this effort and a summary of its national programme merits attention.

5.1.1 Historical Account

In 1918 seven prefectures of Honshu Island were selected for the investigation of intestinal parasitic infections using mass faecal examination by the direct smear method. By 1922, the prevalences of *A. lumbricoides*, hookworms and *T. trichiura* were established as 70.1%, 28.0% and 56.9%, respectively. The Parasite Control Law was enacted in 1931 and the National Control Programme based on mass stool examination and mass treatment was launched. Health education was intensified. Sanitation was enhanced by introducing new systems of latrine construction. The programme was marked by the gradual decrease in prevalence and by 1941 the rates were reduced to 34.7% for *A. lumbricoides* and 8.9% for hookworms.

The government could not sustain the programme during the Second World War. By 1949, the nation-wide faecal examinations survey reported an overall prevalence of 73.0% for intestinal nematodes: *A. lumbricoides* (62.9%), *T. trichiura* (50%); hookworms (3.5%). Voluntarily in Non-governmental Organizations (NGOs) took the initiative, private laboratories were established, stool examinations were carried out and treatment with anthelmintic drugs began. Primary and secondary school children were targeted, then the activities were expanded to the community as a whole. School children regularly underwent mass stool examination and received treatment twice a year. In 1955, the Japan Association of Parasite Control was founded and, the government passed the School Health Law in 1958 and issued guidance on control technologies. The cellophane thick smear method (to become Kato Katz technique) was invented and was widely adopted for stool examinations. The prevalence of *A. lumbricoides* dropped to 0.9% that of hookworms to 0.0%, and that of *T. trichiura* to 0.25% by 1990.

5.1.2 Tripartite Co-operation

One of the determinants of the successful parasite control programme in Japan was the co-operation between the government, experts in academic circles and the voluntary sectors. Each party had its role with the NGOs as the implementing body. The NGOs established their activities on a fee-charging system which enabled them to continue expand and sustain their activities on a self-supporting basis. The government encouraged the NGOs and empowered them by legislation of the Parasite Control Law and the School Health Law and issued the appropriate guidance for control programmes. The academic groups contributed by providing epidemiological data, by developing examination methods, improving anthelmintics and in training the necessary staff to improve and maintain the quality of techniques.

5.1.3 Japanese Organization for International Co-operation in Family Planning (JOICFP)

In 1974, JOICFP started, in co-operation with the Japan Association of Parasite Control, to promote integration of the control of intestinal nematode infections with family planning and nutrition. This was proposed to utilize fully the benefit of parasite control programmes as the entry point for other public health measures. It was recognized that an intestinal helminth control programme is simple and easily implemented, in addition to having a direct, immediately visible effect. The idea was accepted by family planning programmes in many countries and they operated parasite control programmes themselves by establishing their own laboratories. After introducing the parasite control programme as the focus for integration it was found that family planning activities could be promoted more easily. The integration approach has been introduced in Asia and Southeast Asia, Latin American and in Africa. By April 1996, 25 countries were operating JOICFP projects successfully.

5.2 Control of soil-transmitted nematodes in areas of low prevalence: Seychelles experience

The Seychelles archipelago comprises 115 islands with 73,000 inhabitants, but most live on the main islands of Mahe, Praslin and La Digue. The budget for health per capita was 280 US\$ in 1994. Education covers over 95% of the school-eligible age group. A school health programme is implemented by nurses from nearby health centres and a health education programme (Social Education Programme) is also carried out by specially trained teachers. Treated water supply is utilized by 70% of the population and only 5% of the population lacks latrines.

5.2.1 Planning, coordination and management

In consultation with the Ministry of Health, a plan of action was devised, with the objective of reducing the intensity of intestinal nematode infections to a level which no longer constituted a public health problem. The specific control objectives within a three-year span were: (i) reduction of intensity (epg) of infections with *A. lumbricoides* by 60%, and of *T. trichiura* and hookworm infections by 30% in school-age children, (ii) reduction in the target population of prevalence of *S. stercoralis* infection by 30% and (iii) reduction in the target population of prevalence of amoebiasis of 40%.

School children and pregnant women represented the target groups. A survey to collect baseline data on prevalence and intensity of intestinal parasitic infections was necessary to better define the targets of the control programme and to have a solid basis for monitoring and evaluation of outcomes. After having trained the health staff (school health nurses, environmental health officers, laboratory technicians) and the teachers in the integrated approach, stool samples from 5% of all school-children were examined by the Kato-Katz technique to identify and count nematode eggs, and by the formol-ethyl acetate concentration technique to detect protozoa and *S. stercoralis* larvae. Quality control was performed at the central level by randomly examining 10% of the total slides. The same children were interviewed to assess knowledge of intestinal parasitic infections before intervention. Pregnant women attending ante-natal clinics had their stools examined for helminths and protozoa and haemoglobin levels determined as a measure of iron status.

Sixty percent of children were infected with one or more intestinal parasites, with significant variation by region. *Trichuris trichiura* was the most common parasite with a prevalence of 53.3%, followed by *A. lumbricoides* with a prevalence of 17.7%. Hookworm infections were present in 6.3% of school children and in 8.6% of pregnant women. Only 14% of women had a haemoglobin level below 110 g/l, 1% had Hb below 80 and none had Hb below 70 g/l. No correlation was found between the intensity of hookworm infection and blood haemoglobin concentration among these pregnant women.

5.2.2 Control measures: Periodic chemotherapy and health education

School children were dewormed every four months in the first year, with a coverage rate of 99.4%. Mebendazole (500 mg tablet), given as a single dose, was the anthelmintic chosen by the Ministry of Health due to the high prevalence of *T. trichiura*. Treatment was delivered by teachers under the supervision of staff from the nearest health centre. Due to the low prevalence of infection in pregnant women, selected treatment was given to positive cases as diagnosed by a routine stool examination. Treatment was administered after the first trimester of pregnancy.

It was recognized in the Seychelles that long-term control of intestinal parasitic infections would be strengthened by a change in health behaviour. Print media (newspaper, posters, leaflets) and electronic media (radio, television, audio-visual aids) were extensively used to increase public information and awareness on intestinal parasites control. Since the start of the programme, education about preventive measures on intestinal parasites was included in the school curriculum. Mobile health teams (environmental health officers, school health nurses), in collaboration with Social Education teachers, organized sessions and disseminated health messages in all schools. The radio advertised the programme's activities and general preventive measures. TV and the national newspaper were also involved in advertising chemotherapy campaigns. A video on prevention and control of intestinal parasites produced in the Seychelles was widely distributed to schools, health centres and broadcast by local TV. Leaflets and posters on the prevention and control of intestinal parasitic infection were designed in Creole and printed locally.

5.2.3 Monitoring and sustainability

After 3 chemotherapy campaigns, the first parasitological evaluation was performed in a sample of about 100 children from each school with the aim of monitoring the reduction in prevalence and intensity of infection. Results showed that the cumulative prevalence of intestinal parasites dropped from 60.5% to 33.8% in the children. The mean egg counts (intensity, epg) was reduced by 85%, 53% and 32% from the baseline value, for *A. lumbricoides*, *T. trichiura* and hookworm, respectively.

5.3 Control of soil-transmitted nematodes in areas of high prevalence: Zanzibar experience

Zanzibar comprises two main islands of Unguja and Pemba, located in the Indian Ocean off the coast of mainland Tanzania. The population is about 700,000 with most living in rural villages. Sanitation coverage is about 75% in urban areas and about 12% in rural areas. Only 3.2% of the rural population has access to piped water supply. The infant and under 5 mortality rates are 120/1000 and 202/1000, respectively, and the maternal mortality rate is 300/100,000. About 40% of children suffer from chronic malnutrition. The health budget per capita is about 1 US\$ p.a.

5.3.1 Planning, coordination and management

Control began on Pemba in 1986, aimed first to reduce morbidity due to *Schistosoma haematobium*. That programme proved highly successful and is continuing with yearly "test and treatment" surveys in school children using reagent strips for diagnosis and Praziquantel for treatment. Within this programme, epidemiological surveys to assess the distribution and intensity of intestinal helminths were also undertaken. A community survey was performed in 1991 on 2200 individuals of all ages from 8 different villages of the island. A total of 1,120 school children from standard 5 in 35 schools were examined in 1992. Intestinal nematode infections were confirmed as a major public health problem among school children with a prevalence of 99.7%. In Unguja, intestinal nematode infections have come into focus as a important public health problem, the prevalence of intestinal nematode infections was 85% in a survey of over 3,000 school children.

A trial comparing the efficacy of albendazole (400 mg) single dose and mebendazole (500 mg) single dose was carried out in Pemba in 1993 (Albonico *et al.*, 1994). Cohorts of children were followed at four and six monthly intervals after treatment to evaluate rates of reinfection. Since Pemba is a highly endemic area for soil-transmitted nematodes, it seemed likely that a high proportion of the children would acquire new infections in the 4 months following treatment. This situation had significant implications for health planners requiring them (a) to design appropriate treatment schedules to control morbidity and (b) to choose the most cost-effective drug. Both drugs have similar efficacy in reducing intensity of infections, and treatment with either drug did not prolong the interval of reinfection. Cost was the major determinant for choosing mebendazole 500 mg and a single dose every four months was selected as standard treatment after having confirmed the good quality and *in vivo* efficacy of the generic mebendazole used.

With approval from the Government of Zanzibar, school-based control activities began in 1994 with a team of health officers working in close collaboration with teachers. The aims of the programme were to reduce the intensities (measured as epg) of *A. lumbricoides*, hookworms and *T. trichiura* by 60%, 30% and 20% respectively, in a target population of 70,000 school children. Recognizing the need for action to improve the health and well being of Zanzibari children, the Government introduced the five-year National Programme of Action (NPA) whose main objective is the survival, protection and development of Children of Zanzibar.

5.3.2 Monitoring and evaluation

Results from the first year of evaluation were encouraging: by treating school children with mebendazole (500 mg every 4 months), the prevalence of severe anaemia due to hookworm infection was reduced by 39% and the prevalence of iron-deficient erythropoiesis by 16% after one year. These improvements were related to significant reductions in the intensity of soil-transmitted nematode infections. Intensities were characterized by important seasonal variations but prevalences changed little. These findings suggest that it is important i) to perform monitoring and evaluation in the same season; ii) in high transmission areas, intensity (and not prevalence) is the reliable indicator to monitor the impact of periodic chemotherapy and iii) a more effective treatment regimen might be necessary during any high transmission season (Albonico et al., 1995).

For the initial monitoring of the impact of periodic chemotherapy, about 1,000 children from primary schools (standards 1,2,3, and 4), treated with mebendazole every four months, were followed for 1 year. For future monitoring (in 1996-1997), 600 children from standard 4 in the same schools will be selected. A sample of equal number of children just enrolled in school, will be examined to account for secular changes in iron status not related to the deworming programme, and also to monitor any change in prevalence and intensity in the child population that was not treated, as an indicator of transmission of the infections. For that sample of children, nematode infection (by the quantitative Kato-Katz thick smear technique), iron status (by haemoglobin, erythroporphyrin and serum ferritin) and growth (weight and height) will be assessed.

5.4 Use of anthelmintic chemotherapy in high risk groups in Sri Lanka

In most developing countries, the two groups at highest risk of morbidity (and mortality) due to soil-transmitted nematode infections are children and pregnant women. In Sri Lanka over 50% of children have one or more soil-transmitted nematode infection. Studies on pregnant women in Sri Lanka have detected prevalences of iron-deficiency anaemia ranging from 56-78%.

5.4.1 Children and provision of anthelmintic chemotherapy to children

There are about 10,000 state schools and approximately 100 private schools in Sri Lanka. There are about 2 million pre-school children and a similar number attending primary schools. Pre-school children have access to Well-baby clinics where in addition to routine health check-ups, nutritional supplements are provided. De-worming is one of the activities of Well-baby clinics, but if anthelmintic drugs are not available at the clinics, mothers are encouraged to buy the drugs for their children.

The State Pharmaceutical Manufacturing Corporation (SPMC) of Sri Lanka manufactures mebendazole 100 mg and 500 mg tablets at low cost. A blind study to evaluate the relative efficacies of mebendazole (SPMC) 500 mg, mebendazole (Vermox®) 500 mg, and albendazole (Zentel®) 400 mg revealed no difference between the efficacy of SPMC mebendazole 500 mg and Vermox® 500 mg. Albendazole (Zentel®) 400 mg was found to be superior to both brands of mebendazole in its efficacy against hookworm infection (*N. americanus*); however, substantial ERRs of approximately 75% were obtained with both brands of mebendazole. Regular deworming with mebendazole should thus be expected to have a significant impact on lowering the intensity of hookworm infection in a community.

About 80% of the schools participate in the School Medical Inspection programme during which staff visit schools annually and children in standards 1,4 and 7 are given a health check up. At this visit all children in year 1 are given a course of mebendazole (100 mg twice daily for 3 days). Parents, present during the school medical inspection, are given talks on the harmful effects of soil-transmitted nematodes and the preventive measures that should be taken. They are also encouraged to deworm their children periodically. Replacement of the

3-day regimen with a single dose of mebendazole 500mg is expected to ensure greater compliance.

Nearly one million people live and work on tea, rubber and coconut plantations in Sri Lanka. Although substantial investments have been made in the plantations to improve living conditions, a large segment of the population still has to contend with poor housing, inadequate sanitary facilities and limited access to safe water. Soil-transmitted nematode infections are widely prevalent in these communities. In 1992, 89.7% of children from 3 to 12 years and 86.2% of women of childbearing age were found to be infected with at least one kind of soil-transmitted nematode infection. Of the women, 41.4% were infected with hookworm with the majority having light or moderate infections.

In 1994, a control programme was launched in the plantations, targeting more than 200,000 children. A single dose of mebendazole 500 mg (SPMC) is given to all children biannually. So far 4 rounds of treatment have been given and an evaluation has been carried out 5 months after the second round of mebendazole 500 mg (ie. one month prior to the 3rd round of deworming). The results indicate that there has been a low to moderate decrease in both prevalence and intensities in all 4 estates. Intensities of infection were found to have decreased more in the two low country estates compared to the up country estates. This was not unexpected because in the up country estates housing is more crowded and the soil tends to be more polluted in than the low country estates where housing is more scattered.

5.4.2 Provision of anthelmintic chemotherapy to pregnant women

Women of reproductive age continue to have a high prevalence of anaemia particularly during pregnancy. Although nutritional anaemias are by far the most common and linked mainly to iron and folate deficiencies, chronic gastrointestinal blood loss as seen with hookworm infection is also important. Consequently, the prevention and control of soil-transmitted nematode infections should play an important role in the prevention of anaemia in pregnancy.

As part of a National Strategy for the prevention and control of anaemia in pregnancy, all pregnant women are offered a single dose of 500 mg mebendazole at the earliest antenatal visit after the first trimester. At first the regimen was

100 mg twice a day for 3 days, but the single dose preparation now given ensures better compliance and is cheaper. In addition as part of the National Strategy to control anaemia in pregnancy, supplements of iron, folate and vitamin C are provided to be taken on a daily basis, and emphasis is placed on imparting appropriate health messages. Since undernutrition and anaemia among women have been a problem in the plantations, all pregnant women in the plantations are now routinely given mebendazole 500 mg during their first visit to the antenatal clinic after the first trimester. In the plantations, anthelmintic drugs are available for sale and adolescent girls are encouraged to take anthelmintic drugs to relieve them of hookworm infections. The impact of this major public health intervention will be evaluated in 1997.

5.5 Monitoring large-scale integrated control programmes: the Mexican experience

Since 1993, the National Health System in Mexico has organized periodical health campaigns, known as "National Health Weeks" (Semana Nacional de Salud) which promote various interventions focused mainly on children, including distribution of oral rehydration packages, training of mothers in diarrhoea treatment, administration of megadoses of vitamin A and EPI vaccinations. Identification of the public health importance of infection by soil-transmitted nematodes in Mexico and the availability of low toxicity drugs which can be administered in a single dose, led to the inclusion of mass anthelmintic chemotherapy (albendazole) in National Health Weeks.

5.5.1 Objectives of the intervention

The principle aims and expected outcomes of the programme have been:

- To provide anthelmintic chemotherapy for 95% of children aged 2 to 14 years in municipalities with high risk of intestinal infections.
- To reduce the frequency of severe complications, including mortality associated with soil-transmitted nematodes.
- To decrease the harmful impact of nematode infections on the growth, development and school achievement of children.

- To decrease the egg output from soil-transmitted nematodes among groups with highest infection prevalence.
- To decrease the prevalence of infection among school age children living in specific areas (municipalities with high risk of intestinal nematode infections).
- To decrease the reinfection rates among school-age children living in areas receiving mass anthelmintic chemotherapy.

The target groups for administration of albendazole were children from 5 to 14 years (weeks 1st and 2nd) and from 2 to 4 years (weeks 3rd, 4rd, and 5th) (approx. ten million children in total). A single dose of albendazole (400 mg), either tablets (5-14 yrs) or suspension (2-4 yrs), was administered every four months (October 1993, February 1994, June 1994, October 1994 and February 1995). Albendazole was purchased by the Ministry of Health through a consolidated contract at a cost of 11 US\$ cents per treatment.

5.5.2 Social and community mobilization

The social mobilization included: national, state and county consensus; Participation of private enterprise and NGOs; participation of social and community leaders; TV and Radio (interviews and spots); graphic educational material (posters); "health telegram" one sheet (10 million printed).

5.5.3 Training of health personnel

The actions taken included; informing and training decision makers; training for state trainers (300 epidemiologists and health administrators); design and production of 500 educational packages (videos, 60 slides, manuals); training of operational personnel at local level; training of teachers and volunteers (50,000 approx.).

5.5.4 Surveys and Evaluation

Study sites were selected for survey and evaluation from each of the 21 states that participated in this programme. A questionnaire was designed to record information on geographic and demographic variables of the community

(climate, altitude, latitude, population size, literacy, characteristics of households, availability of piped water). Communities were stratified according to the degree of risk of infection (high, moderate and low). Evaluation of the intervention was accomplished through sentinel stool surveys from a sample of the population before and after each drug administration. Sentinel surveys are not fully representative of the total population, but offer information on groups and sites of interest.

5.5.5 Results

Baseline data were obtained from 9,337 children with stools being examined by the Kato-Katz method. The results showed prevalences for *A. lumbricoides* of 20.9% (range 0-84.9%), for *T. trichiura* of 17.4% (range of 0 to 85.8%) and for hookworm of 0.9% (range 0 to 8.87%). Prevalences of single and multiple helminthiases were found to be associated with climate, latitude and altitude; the risk increased 17 times for residents in tropical locations below 500 m altitude and 16 to 20 degrees North.

During the five weeks, over 50 million doses of albendazole were administered and adverse effects due to the administration of the drug were minimal. Prevalences of soil-transmitted before and after treatment for each "National Health Week" are shown in Table 1 and 2.

Table 1. Prevalence of intestinal nematode infections before and after treatment during "National Health Weeks" in Mexico.

Week	Prevalence (%)	
	Before treatment	After treatment
1st week (October 93)	32.3	13.6
2nd week (February 94)	22.5	10.8
3rd week (June 94)	16.9	5.1
4th week (October 94)	15.5	6.2
5th week (February 95)	14.8	4.8

Table 2. Prevalence and intensity of *Ascaris lumbricoides* infection before and after mass anthelmintic chemotherapy with albendazole in Mexico.

Week	Before treatment		After treatment	
	Prevalence (%)	Parasitic loads geometric means (epg)	Prevalence (%)	Parasitic loads geometric means (epg)
1st week October 93	23	3010	4.1	2
2nd week February 94	14.3	1074	3.5	1
3rd week June 94	8.2	544	1.9	1.2
4th week October 94	7.2	613	1.4	1.1
5th week February 95	9.1	1032	0.9	1.0

5.5.6 Merits

The evaluation demonstrated that mass administration of albendazole to children 2 to 14 years old living in high risk municipalities produced a satisfactory CR of (83% to 93%). A decrease in infection intensity (99.9% counts epg) and cure of moderate and severe cases (92% to 93%) were observed with efficacy having a cumulative effect. Overall, infection with *T. trichiura* was the least responsive to treatment with a single dose of albendazole.

From the perspective of individuals, subjects have rapid clinical improvement in health and well being coupled with a decrease in demand of health services due to soil-transmitted nematodes. It is expected that the nutritional status and school performance of individuals will have improved. From the community perspective there is an increase in interest and support for other national health programmes. As part of its preventive services, the Mexican Ministry of Health has included in its National Health Program (1996-

2000) the administration of mass anthelmintic chemotherapy for soil-transmitted nematodes to children living in high risk areas.

5.6 Developments in the control of *Strongyloides stercoralis*

5.6.1 Previous experience

Compared with the four commonly studied intestinal nematode infections, much less is known about the public health importance of *S. stercoralis*. Morbidity is known to be substantial in individuals immunosuppressed by chemotherapy, radiotherapy or genetic disorders (Genta, 1989). Furthermore, the possibility of autoinfection occurring with this helminth plays an important role in chronic disease leading to increased morbidity among people living in endemic areas. Until recently, treatments for *S. stercoralis* invariably resulted in low cure rates or were hampered by a high frequency of side-effects. Treatment with multiple doses of thiabendazole resulted in CRs of between 65% and 100%, but two thirds of the treated subjects felt nauseous and one quarter experienced neuropsychiatric side-effects (see Grove, 1989). Albendazole has to be administered for at least three consecutive days, as does thiabendazole if significant CRs are to be secured. Although the cure rates for albendazole are generally lower, the rare occurrence and mild nature of its side-effects offer some advantages; albendazole is the drug of choice for treatment leading to a better compliance by the patients.

The introduction of ivermectin as a broad-spectrum, single dose anthelmintic drug, has presented a new option for dealing with a wide range of different intestinal nematode infections, especially for treatment in the community. Previous studies carried out to evaluate the effect of ivermectin on infections of *S. stercoralis* reported efficacies around 85% or above for a single oral dose, but these studies have mostly been carried out on small samples of patients, and a wide variety of therapeutic schemes and doses have been used. Studies of the efficacy of the drug in children, the main target population in many control programmes, are essentially lacking.

5.6.2 Zanzibar experience, 1994

A study was carried out in October-December 1994 in Zanzibar to:

- a) determine the efficacy of a single dose treatment of ivermectin (200 µg/kg of body weight) against *S. stercoralis* in comparison with doses of albendazole (400 mg) administered daily for three days.
- b) compare the efficacy of the two treatments against other intestinal nematode infections;
- c) monitor the frequency and severity of side-effects associated with the use of these drugs.

For subjects entering the trial, a randomized list for the sequential allocation of the drugs was prepared in advance. The individuals were given either the single dose (200 µg/kg of body weight) of ivermectin (Mectizan®, supplied by Merck & Co.) or the first dose of 400 mg of albendazole (Zentel®, SmithKline Beecham). The individuals receiving albendazole treatment were given the second and third doses on the next two days under supervision. Side-effects were reported and monitored.

5.6.3 Results and Conclusions

Treatment of infected children with ivermectin or albendazole resulted in cure rates for *S. stercoralis* of 83% and 45% respectively. While *A. lumbricoides* was effectively eliminated by both drugs (100% and 99%), *T. trichiura* was eliminated only in 11% (ivermectin) and 43% (albendazole) of the subjects, although the mean egg counts were reduced by 59% and 92%, respectively. Ivermectin was not found to be effective against hookworms, while albendazole resulted in a CR of 98%. No severe side effects were recorded and any mild side effects were of transient nature for both treatments. It was concluded that ivermectin provides a safe and highly effective single dose treatment for *S. stercoralis* and *A. lumbricoides*, but it appears not to be an alternative for the treatment of *T. trichiura* and hookworm infections.

6. Approaches to the wider control of helminthiases: opportunities for integration

6.1 Chemotherapy for onchocerciasis

6.1.1 Onchocerciasis

Onchocerciasis is a disease which in its most severe forms, tends to afflict communities which are the most isolated, with little or no contact with national health services, and whose problems may not even be known to the government. Until 1990, there was little that could be done for such communities, unless resources became available to mount vector control operations; national programmes for the control of onchocerciasis were not usually developed. However, the introduction of ivermectin for community-wide distribution has radically altered this picture. The drug is effective in controlling the worst manifestation of onchocerciasis, and is safe enough to be used in large-scale treatment campaigns. With the introduction of ivermectin for the control of onchocerciasis, a number of operational issues had to be addressed, including the need for an (i) efficient, affordable and non-invasive method for identifying onchocerciasis endemic communities, (ii) a means of drug delivery and (iii) systems to promote community compliance.

The task is to determine the most cost-effective and sustainable way to deliver ivermectin to those heavily infected communities, which are at highest risk of blindness, and are located at the "end of the track". Drug delivery approaches have been investigated: clinic-based/passive and community-based/active distribution systems, integration into the PHC approach and recently the community self-treatment approach.

6.1.2 Clinic-based/passive drug delivery

Clinic-based/passive distribution is normally carried out in areas where the occurrence of onchocerciasis ranges from sporadic to hypoendemic. Health professionals working at existing clinics give ivermectin to eligible persons who attend with suspect or evident signs of onchocerciasis. Although this is the simplest and the cheapest of all ivermectin distribution strategies as distribution itself uses only existing personnel and requires no field work, the majority of

people at risk of blindness from onchocerciasis are not reached because they live in remote areas, a long way from the nearest health facilities. Transport from these areas is erratic and relatively expensive, and so few people are able to visit the clinics. Other factors associated with this drug delivery approach include: (1) the absence of any obvious impact/effect on the transmission of onchocerciasis within the community; (2) over-treatment - it is possible that patients may be treated several times in a short period of time through attendance at a health facility (current evidence suggests that receiving several doses of ivermectin over a relatively short period of time is unlikely to have serious side-effects); (3) compliance with re-treatment schedule - patients may not return to the health facility after 12 months for re-treatment.

6.1.3 Active drug delivery

Active delivery refers to the distribution of drugs by mobile teams which travel in vehicles from village to village to give ivermectin at agreed central locations (chief's palace, community hall, market place). Active delivery is expensive and necessitates considerable human and financial resources including regular payment of per diems to health personnel, purchase of fuel, and maintenance of vehicles.

6.1.4 Integration into the PHC

On a sustainable basis, this approach is expected to benefit the health system in general, as well as controlling onchocerciasis. But health centres with the best performances usually reach only 30-40% of population. If the distribution of ivermectin were to be integrated into the PHC system, the coverage might be no better than 40%. Also, the relative importance attached to the development of PHC and the delivery of Ivermectin may differ from area to area.

6.1.5 Community self-treatment of onchocerciasis with Ivermectin

In this promising approach for developing sustainability, the community takes responsibility for the distribution of the drug. This drug delivery strategy confers ownership of the programme to the community and makes the drug available to the community at all times. Operational research is in progress to

study the safety and sustainability of the method as well as its acceptability in different cultural settings.

6.2 Controlling lymphatic filariasis

6.2.1 Tools and strategies

In the past, because of our limited understanding of the importance of lymphatic filariasis and its consequences, treatment tools were cumbersome and unpopular, and control strategies were both costly and poorly effective. Consequently, lymphatic filariasis was discouraging to deal with, both for patients and public health workers. This pessimism has all but disappeared because of an array of critical new developments during the past decade, including:

- new techniques for examining patients (lymphoscintigraphy and ultrasound) have revealed hidden, internal pathology;
- new tools (based on antigen and DNA detection) for diagnosing infection (and monitoring control efforts) that are much simpler and more cost-effective than any available previously;
- new understandings of the social and economic disruption to communities brought on by lymphatic filariasis, beyond the personal suffering of those with disease;
- and, *most importantly*, new treatment tools and strategies that can effectively minimize the suffering of patients, interrupt transmission of infection in the community, and be inexpensively integrated with other primary health care activities.

The new strategy for controlling/eliminating lymphatic filariasis has two major features:

- a focus on treating the human population;

- use of community-wide treatment to replace other forms of drug delivery.

The best treatment options available are:

- a) 1-day, once yearly treatment (for estimated 5-7 years) using any of the following:

- ◇ 2-drug regimens (preferable), 99% reduction in microfilaraemia for >1 year

1) IVERMECTIN (200 µg/kg) plus DEC (diethylcarbamazine, 6 mg/kg)

2) IVERMECTIN (200 µg/kg) plus ALBENDAZOLE (400 mg)

- ◇ 1-drug regimens, yielding 90% reduction in microfilaraemia for >1 year

1) DEC (6 mg/kg)

2) IVERMECTIN (400 µg/kg)

- b) DEC-fortified table/cooking salt as substitute for normal salt

- ◇ use for 9-12 months reduces microfilaraemia by 99% for at least 1 year

6.2.2 Integration of intestinal nematode control and filarial nematode control

The tools and strategies recently developed for filariasis control are similar to those used in controlling intestinal nematodes, the major difference being that the most effective approach to lymphatic filariasis involves the use of 2-drug regimens. This means that in programmes using one drug to treat intestinal nematodes in regions with endemic filariasis, a greater public health impact can be achieved at minimally increased cost by adding a second drug, either

ivermectin or DEC, to treat lymphatic filariasis as well.

It is clear that opportunities may be being missed even now for integrating filariasis control with other on-going large-scale public health programmes. For example, in the African Programme for Onchocerciasis Control (APOC), where single-dose ivermectin is being administered once yearly to 16 countries in Africa. There are also large-scale intestinal nematode control programmes using single-dose albendazole being undertaken in Indonesia, India, Tanzania, Ghana and elsewhere.

Better coordination and the combining of forces and resources would appreciably enhance the health impact of control efforts against these (and perhaps other) helminth infections. Such coordinated efforts, should be more appealing both to Health Ministries and to financial donors because of their greater cost-effectiveness and, because of the better public health product for the afflicted communities.

7. Some operational features of anthelmintic chemotherapy

7.1 Determination of the appropriate interval for chemotherapy

The endeavors of the Asian Parasite Control Organization (APCO) have produced a vast body of knowledge about the design and implementation of programmes to control soil-transmitted nematode infections and related morbidity (APCO 1980, 1983, 1986, 1989, 1993). This body of information is essential reference for those responsible for training health professionals assigned to the control of soil-transmitted nematode infections. Planners must not extrapolate directly from the body of results gained by the APCO or any other control programme; local conditions and circumstances must be taken into account. A key determinant for the optimal use of anthelmintic drugs (reduction of intensity leading to decrease in morbidity and disruption of transmission) is to decide when and how frequently to treat the population of concern.

From extensive studies on the transmission of *A. lumbricoides* carried out by the APCO research programme, it is apparent that determination of intervals of treatment depends on (a) knowledge of rates of reinfection following chemotherapy and (b) detection of the presence or otherwise of seasonal

influences on transmission of infective stages. Seasonal effects can be quite subtle, being related to such activities as the use of nightsoil as a fertilizer at times when particular vegetables are available and in demand (Figs. 7.1 - 7.4).

The appropriate intervals of community treatment should be determined after consideration of epidemiological, pharmacological and socio-economical factors. From the epidemiological point viewpoint, the key results concern the frequency and seasonal variation of reinfection that are to be considered. Ideally, community treatment should be applied soon after an identified transmission season is over.

The conclusion from the body of results obtained by the APCO workers indicates that the appropriate intervals for the application of anthelmintic chemotherapy to control morbidity induced by soil-transmitted nematodes will be twice annually for prevalence rates <50% and thrice annually for prevalence rates >50%. Again, it is stressed that the decision about intervals between treatments must be taken after consideration of local circumstances.

7.2 Delivery of anthelmintic drugs through schools: The Partnership for Child Development

Experience from several control programmes and from the efforts of the Partnership for Child Development (section 2) has shown that treatment targeted at school-age children can reduce the intensity of infection in the remainder of the community which do not receive treatment, indicating that treating school-age children reduces transmission (Asaolu et al., 1991; Bundy et al., 1990). The benefits of periodic anthelmintic treatment of school-age children are now clear.

The fact that children assemble in schools for many days of the year means that many can be treated at once. Secondly, the school system provides an existing infrastructure for delivering treatments. Thirdly, there are usually more schools than clinics and more teachers than health personnel so the potential exists for treatments to be delivered to schools and be administered by teachers. Fourthly, school-based health programmes have the potential to integrate anthelmintic treatment against soil-transmitted nematodes with actions for other diseases such as schistosomiasis and to treat micronutrient and vitamin deficiencies. Schools can also provide health education to support control

programmes with the aim of attempting to change behaviours to reduce or even prevent transmission. Delivering anthelmintics through schools is relatively inexpensive and, cost-effective and in circumstances where enrolment in schools is good, such programmes are likely to achieve effective coverage.

A limitation of school-based programmes is that they do not reach children who do not attend school, either because they have never enrolled or because they have dropped out. Such children will be disadvantaged not only because they do not benefit from school education, but also because they miss school health programmes. Schools have the potential to act as a focus for health services for children out of school; efforts are needed to promote this service. The Partnership for Child Development and WHO are presently assessing alternative means to reach non-enrolled school-age children.

8. Awareness of the potential threat of drug resistance by soil-transmitted nematodes and other helminth infections

Drug resistance is defined as a genetically transmitted loss of sensitivity for a drug in a parasite population which was previously sensitive to the appropriate therapeutic dose. As yet, there is no unequivocally confirmed report of drug resistance in a soil-transmitted nematode infection of humans to the currently used anthelmintic drugs.

The existence of drug-resistant populations of soil-transmitted nematodes is commonly reported in the 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. That drug resistance should emerge should not be unexpected; the genes involved will already exist in the different nematode populations. The fundamental strategy is to apply chemotherapy so that the emergence of drug resistance is delayed or circumvented while health benefits continue to accrue. Also, it seems prudent to develop a protocol to investigate suspected drug resistance. In due course, this task might be coordinated by WHO so that guidelines can be incorporated as part of best practice for monitoring the progress and sustainability of control programmes.

8.1 Theoretical considerations

A theoretical approach to the consideration of the problem of drug resistance in helminths is based in its simplest form on five assumptions: i) that helminth populations are closed so there is no gene flow; ii) that universal anthelmintic treatment is applied; iii) that treatment is homogeneous; iv) that two alleles are involved; v) that continual selection pressure is applied. Under these conditions, it should be only a matter of time before drug resistance for soil-transmitted nematodes will appear, the most crucial factor being the generation time of the nematode species of interest. By reference to studies on the development of pesticide resistance in insects (see Comins, 1977), it seems that from 5-100 generations would be required under appropriate conditions before drug resistance would arise in a nematode population.

Theory also indicates that since the relative flow of genes through generations is crucial for the development of drug resistance, several steps can be taken to delay and even avoid the problem. For example, treatment of a proportion of the people in an infected community (e.g. drug targeted at school children) will ensure that some nematodes remain in the community and that the genes of these survivors will dilute those of the nematodes experiencing the selection pressure. Treatment given at intervals greater than the nematodes' generation time will act against drug resistance. Density-dependent constraints of the fecundity of individual female worms will tend to dampen the development of drug resistance. Also, changing the drug of choice during a particular control programme will also reduce the degree of selection pressure on the population of nematodes.

8.2 Experience of anthelmintic drug resistance in nematodes of veterinary importance

The economic importance of endoparasitic nematodes in animals grazed on grass has resulted in the widespread use of anthelmintic drugs to improve productivity and prevent disease and death. Because of the cost of diagnosing individual infected animals, whole flock or herd treatment has been the normal practice and leading to the accelerated development of populations of nematodes resistant to modern anthelmintic drugs. Resistance is of major concern to the small ruminant industry worldwide, particularly where sheep are kept in subtropical/tropical regions and the highly pathogenic bloodsucking nematode

Haemonchus contortus limits production. Pyrantel resistance is beginning to emerge in nematodes infecting horses.

8.2.1 Recognition of drug resistance

The first step in the management of drug resistance is to be able to detect resistance when it occurs and distinguish it from drug tolerance. A variety of procedures has been developed for use by veterinarians, but of these probably only the Faecal Egg Count Reduction Test has any application at present in developing countries. Use of this type of test, however, depends on agreed protocols and agreed efficacies for the drugs in current use. The immediate lessons to be learned from the veterinary situation are first, there is a need to develop robust and reliable tests to confirm or refute suspected drug resistance under the conditions occurring in developing countries. Secondly, if drug resistant populations of soil-transmitted nematodes are found in humans, attempts should be made to establish the worms under laboratory conditions for research purposes.

8.3 Experience of anthelmintic drug resistance in schistosome populations

The three drugs currently recommended by the WHO for use against schistosomes are praziquantel which is effective against all species and to a lesser extent metrifonate and oxamniquine which are effective against *Schistosoma haematobium* and *Schistosoma mansoni*, respectively. So far no evidence of drug resistance to metrifonate has been reported. In the case of oxamniquine (and the closely related hycanthone), drug resistance has been encountered both in the field and laboratory since the 1970s. Cross-resistance has not been found between praziquantel, oxamniquine and metrifonate. Any infection uncured by one drug may still be successfully treated with an appropriate alternative drug.

8.3.1 Monitoring drug usage and surveillance for emerging drug resistance

Procedures now being developed to detect emerging drug resistance in schistosomes should be considered by health professionals concerned with the control of soil-transmitted nematode infections. Praziquantel is administered to

millions of people in endemic countries. In Egypt, where more than 20 million people have been treated with praziquantel since 1988, a number of initiatives are underway to monitor for emerging drug resistance. A network of scientists and policy makers from endemic countries and Europe is being formed to investigate 'Patterns of praziquantel usage and monitoring of possible resistance'. The aim of this network is to provide a framework for the rational answer to numerous questions that are relevant to anti-schistosomal chemotherapy with praziquantel. The specific objectives of this network are:

- to collect available data on existing national realities, focusing not only on the chemotherapy programmes supported by national and international organizations, but also on the real situation at the periphery;
- to review and analyze this data, and address all issues related to praziquantel use and drug resistance;
- to standardize a protocol for monitoring resistance;
- to select and possibly equip a number of reference centres to process samples from carriers of resistant schistosomes;
- to ensure that the partners provide practical laboratory support to continue in-depth study of strains arising from the resistance monitoring;
- to formulate policies to assist national health authorities to deal with any occurrence of drug resistance in their countries.

This system can be easily adapted to monitor usage of anthelmintic drugs used in the control of intestinal nematode infections and to establish surveillance models should drug resistance emerge.

9. Recommendations

1. Actions to control soil-transmitted nematodes should be either integrated into existing health care programmes or included when planning new integrated

programmes. Integration between sectors is vitally important for the success and sustainability of any form of community health care.

2. Since the control of soil-transmitted nematodes has been shown to have wide acceptance in the community and to satisfy a need perceived by very many people, health planners are recommended to strengthen existing programmes by adding treatment for soil-transmitted nematodes. Also, health planners are advised that the launch and success of new programmes will be strengthened if chemotherapy for soil-transmitted nematodes is included.
3. Before a control programme aimed at soil-transmitted nematodes begins, an epidemiological survey is advisable, but available resources must be taken into account. The key tool of the survey should be the Kato-Katz examination of stool samples before the first round of treatment. This procedure enables the prevalence and an indirect measure of infection intensity (egg counts) to be made. Knowledge of baseline egg counts relates to morbidity, enables nematodes to be identified, allows targets to be set, permits drug efficacy to be checked and assures that programmes can be monitored and sustained. Most importantly, intensity relates to morbidity and reduction of intensity is the key to a successful control programme.

It is recognized that some health authorities will not have sufficient resources to carry out the ideal survey. This should not discourage a control initiative and data collection may be restricted to children aged 8-15 years because they are often at the greatest risk of infection and morbidity.

It is strongly recommended to use resources mainly on the baseline survey and thereafter on restricted monitoring of the progress of the programme. Although desirable under certain circumstances, there is no need to apply diagnostic screening of individuals before or during chemotherapy.

4. Three strategies are recommended for the use of anthelmintic chemotherapy for the treatment of infections of soil-transmitted nematodes in the community.

- **UNIVERSAL** - population level application of anthelmintic drug in which the community is treated irrespective of age, sex, infection status or other social characteristics.
- **TARGETED** - group level application of anthelmintic drug where the group may be defined by age, sex or other social characteristics irrespective of infection status.
- **SELECTIVE** - individual level application of anthelmintic drug where selection is based on diagnosis of current infection.

(**Note:** Anthelmintic drugs for the treatment of soil-transmitted nematodes in community control programmes must have been recommended by the World Health Organization, must be used according to the manufacturer's instructions and must be of guaranteed quality.)

5. In areas where epidemiological surveys have demonstrated that soil-transmitted nematode infections are endemic, resources for control may be directed at populations or groups (eg. school-age children, pregnant women, adolescent girls, pre-school children, plantation workers, miners) judged to be at risk of morbidity (eg. growth retardation, iron-deficiency anaemia, life-threatening complications).
6. Since morbidity is related to the intensity of infection, targets should be set that are easily monitored. This is an essential activity for assessing progress, estimating needs for sustaining the programme, community feedback and promoting health education.

10. Topics for operational research

In order to advance the extent, success and sustainability of the use of chemotherapy as a frontline activity for the control of morbidity due to infection with soil-transmitted nematodes, the Consultation urges the World Health Organization to co-ordinate the following programme of operational research.

1. Investigate methods for providing planners with systems for measuring, recording and investigating the topographic and climatic distribution of soil-

transmitted nematodes.

2. Prepare guidelines to enable planners to estimate the costs of integrating soil-transmitted nematode control into existing health care in comparison with the costs of freestanding programmes.
3. Develop guidelines for setting targets for control programmes and for determining the frequency of applications of anthelmintic treatment for initiating and sustaining control programmes.
4. Additional information should be provided to planners to facilitate the assessment of morbidity and mortality in relation to the intensity of soil-transmitted nematode infections.
5. Establish data files to record and investigate the efficacies of the individual WHO-recommended drugs for the treatment of each species of soil-transmitted nematode of interest. It is suggested that this task is co-ordinated in consultation with the research-based pharmaceutical industry.
6. The development of new chemical entities for the treatment of soil-transmitted nematodes should be encouraged and the possible use of already approved compounds from the veterinary field should be encouraged.
7. Develop laboratory-based tests to identify and investigate the efficacy of anthelmintic drugs used for the treatment of soil-transmitted nematodes in addition to regimes based on faecal egg counts.
8. Strengthen and widely disseminate advice and protocols for evaluating the quality of compounds marketed as anthelmintic drugs for the treatment of soil-transmitted nematodes.

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