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Report of the WHO Informal Consultation on hookworm infection and anaemia in girls and women

Geneva
5–7 December 1994

World Health Organization
Geneva
Schistosomiasis and Intestinal Parasites Unit
Division of Control of Tropical Diseases
(Formerly: Programme of Intestinal Parasitic Infections of the Division of Communicable Diseases)

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Les opinions exprimées dans les documents par des auteurs cités nommément n'engagent que lesdits auteurs.

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Opening Address

Iron deficiency and anaemia affect a significant part, and usually a majority, of the population in many countries. Most of those affected are women of childbearing age. Women in developing countries spend up to half of their reproductive lives pregnant or lactating. Iron deficiency in childbearing women increases maternal mortality, prenatal and perinatal infant loss and prematurity. Forty percent of all maternal perinatal deaths are linked with anaemia. Favourable pregnancy outcomes are 30% to 45% less likely in anaemic mothers and their infants have less than one-half of the normal iron reserves.

Hookworm infection is a recognized major contributor to iron deficiency anaemia in women of childbearing age in most developing countries and is known to be associated with high maternal mortality and morbidity. However reliable estimates of hookworm infection in women of childbearing age are not available and strategies for the prevention and control of hookworm anaemia in pregnancy are not clearly defined. In spite of recent recommendations for promoting the use of anthelminthics in pregnancy by a WHO meeting in Brazzaville in 1989 and the United Nations ACC/SCN in 1991, there is still no general consensus on the possible impact that control measures may have on maternal and child health and the risks and benefits of the use of anthelminthic drugs associated with iron supplementation in pregnant women.

Blanket exclusion of pregnant or lactating women from treatment against hookworms has been the result, not of clear evidence of possible untoward effects, but of reluctance and fear to carry out appropriate trials on hookworm infection in pregnancy. There is an urgent need to evaluate appropriate treatment against hookworm infection for women of childbearing age so that health services in endemic countries can offer them better treatment according to scientific evidence.

Hookworm infection was the target of major control campaigns from the early years of this century until after the Second World War, yet stubbornly remains as a marker of deficiencies in sanitation, health education and appreciation of its significance as a public health problem. Lack of interest in control at the country level is doubtless a function of the low mortality from hookworm infection in the general population combined with the technical difficulties of measuring and quantifying the morbidity directly due to hookworms compared with that due to concomitant complications such as poor nutrition or retarded rates of growth.

Studies on human hookworm disease and in particular hookworm anaemia have been relatively infrequent since some classical studies by Gilles and by Roche and Layrisse in the '60s. Since 30 years have elapsed and modern investigation methods in the field of gastroenterology, haematology and molecular biology have been introduced, the time has come for a reappraisal of the problem as it affects individuals at high risk of disease, such as women of childbearing age, in various endemic areas of the world.

We have now available safe, broad spectrum, single dose treatment at very low cost for the intestinal nematodes. We understand the ways that deworming affects the health of children of school-age including the effect on school performance. We are completely ignorant with regard to women of childbearing age.

This Informal Consultation is an attempt to readdress the somewhat negative image that hookworm infection in women is an area unworthy of scientific interest and control effort. Several issues, as you will see from the draft agenda, are relevant to the formulation of a comprehensive policy for further research in this field and for the control of hookworm infection in women of childbearing age.

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

Dr Ralph H. Henderson
Assistant Director-General

1. Introduction to the consultation

Recent WHO estimates suggest that approximately 1.4 billion, 1.2 billion and 1 billion persons are currently infected with *Ascaris lumbricoides,* the hookworms (*Ancylostoma duodenale* and *Necator americanus*) and *Trichuris trichiura* respectively. Our WHO Collaborating Centre in Oxford has estimated 214 million cases of ascariasis, 130 million cases of trichuriasis and at least 98 million cases of hookworm disease causing clinically demonstrable morbidity with the negative effects of chronic infections on growth, nutritional status, physical fitness, physical activity and also school performance of children.

It has been demonstrated that children of school-age are the group who usually harbour the heaviest intensity of infections of *Ascaris* and *Trichuris.* In the school population, a control programme targeted at particular parasite species is surely out of place with the present broad spectrum anthelminthics. We have also evidence that the consequences of chronic infections in these children are promptly reversed by treatment with broad spectrum anthelminthics.

Chemotherapy will induce sustained reductions in worm burdens, if given at regular intervals for an appropriate period. The beneficial effect on growth, nutrition, physical fitness and cognitive function in children has been demonstrated both with albendazole and more recently with mebendazole. Studies are under way in various countries in collaboration with the Partnership for Child Development to assess the impact of deworming of school children; studies have been undertaken with support from TDR to evaluate the risk and benefits of concomitant administration of praziquantel and albendazole in several countries; and finally studies are under way in a collaboration between WHO, the Johns Hopkins University and the Government of Zanzibar to assess the impact of different retreatment intervals with mebendazole 500 mg on the nutritional status of schoolchildren. We are actively engaged in developing an effective comprehensive strategy for the control of morbidity due to the hookworms, *Ascaris* and *Trichuris* in the school age population.

The prevalence and intensity of hookworm infection show a slower rise with age than those of *Ascaris* and *Trichuris.* In general more adults than children will be infected and the adults will have, again in general, the larger worm burdens.

Adolescent girls and women of child bearing age will generally be more heavily infected than younger boys and girls with either *Ancylostoma* or *Necator* or even both species. Two of the questions that we will seek to answer in the next three days are what do we know of the impact of hookworm infection in adolescent girls and women of childbearing age and what do we need to learn?

The World Health Organization recommends mass treatment with broad spectrum anthelminthics in areas where the prevalence of geohelminth infections exceeds 50% in the school-age population. More recently we have recommended treatment, with single dose mebendazole, in malnourished and anaemic children between 2 and 5 years, in areas of high transmission of hookworm and *Trichuris*. These recommendations will be included in the sick child initiative charts that are presently under preparation by WHO.

Today we have experts in the field of nutrition, parasitology, toxicology and pharmacology, and representatives from endemic countries and various drug companies. We need your recommendations for the women of childbearing age. Can drugs be given safely in this group and, if yes, when should women be treated?

A recent study in Sri Lanka has shown that therapy with anthelminthics after the first trimester, as recommended by the Ministry of Health of Sri Lanka, was accompanied by a significant increase in the iron status of women when associated with iron supplementation. What is our confidence in using anthelminthics in this population group? Based on the experience from Sri Lanka, what do we know and what do we still need to know?

Rose in 1920 in his sixth annual report of the International Health Board of the Rockefeller Foundation, wrote the following, based on experience with the Foundation's hookworm campaigns:

It is probable that hookworm disease has a deterent effect upon the birth rate. Not only do sterility and impotence commonly caused by the infection reduce the frequency of conception, but the effects of the disease, falling most heavily on women of childbearing age, cause a large proportion of pregnancies that do occur to terminate in abortions and miscarriages. Whenever treatment is carried out over a large area, the birth rate is stimulated to a marked degree. Many women become pregnant who have not borne children for years. The regularity of menstruation is restored, sterility reduced, the number of pregnancies correspondingly increased, and the proportion of unfavourable terminations reduced.

In other reports from Australia of the 1920s and from China of the 1940s, arrested sexual development in children, impotence in adult males and amenorrhoea in adult females are listed as consequences of heavy hookworm infection and prolonged anaemia. Demonstrations of the deleterious effects of mild hookworm-associated anaemia in large scale, population-based studies are lacking and only a few small studies have found an association with premature delivery and low fetal birth weight. We need urgently to carry out research on hookworm infection in pregnancy, as stated earlier by Dr Henderson. You have the task, in the next three days, also to set the priorities for this research to take place. I look forward very much to sharing the next three days with you and receiving your advice.

Dr Lorenzo Savioli
Programme of Intestinal Parasitic Infections

2. *Ancylostoma duodenale* and *Necator americanus*

Recent estimates suggest that at least one billion people are currently infected with *Ancylostoma duodenale* and *Necator americanus*, with the latter species being responsible for most of the infections. These species of hookworm, together with *Ascaris lumbricoides* and *Trichuris trichiura*, make up the quartet of common soil-transmitted helminths which flourish where poverty, poor nutrition, inadequate sanitation, shortage of clean drinking water and minimal health care prevail. Hookworms are usually more abundant in rural as opposed to urban communities.

2.1 Life history

The hookworms are nematodes with a direct life cycle. In the case of *N. americanus*, transmission and infection depend on the penetration of human skin by third-stage larvae which develop from eggs passed in human stools into the environment. Third-stage larvae of *A. duodenale* also develop in the same way as those of *N. americanus*, but *A. duodenale* is an opportunistic species whose larvae can establish an infection on being swallowed or, may occasionally pass the placenta and invade the foetus *in utero* (see section 4). Transplacental migrations are known to occur with other species of nematode in animal hosts and, in some cases, this process is related to the physiological stimulation of arrested larvae in the tissues of the host. There is strong circumstantial evidence to show that larvae of *A. duodenale* can become arrested in people exposed to them in parts of Asia (China and India). Transmammary transmission is known to occur for many species of animal parasitic nematodes and has been suggested to explain a large percentage of all human neonatal *A. duodenale* infections (see section 3 and 4).

After completing a period of migration through the tissues, larval hookworms return by means of the respiratory system to the alimentary tract. The jejunal mucosa appears to be the preferred habitat where the maturing larvae and adult worms bite into the tissues and feed on blood. Hookworm feeding activity involves the secretion of anticoagulant so that feeding lesions continue to bleed even if the worm is not pumping blood at the time. It has been estimated that a single *N. americanus* is responsible for a mean ($\pm$ SD) blood loss of 0.031 $\pm$ 0.015 ml per day. Similar evidence suggests that an *A. duodenale* will cause a mean blood loss of about 0.08 $\pm$ 0.02 ml per day. These measurements of feeding activity explain the pathogenicity of hookworms and account for their contribution to the development of iron deficiency anaemia. Plasma proteins, micronutrients such as zinc and other compounds are also discharged into the gut lumen as a result of hookworms' feeding.

The key to understanding the chronic disease caused by hookworms is directly related to the number of worms per host. Heavily infected individuals will be most at risk from the consequences of iron-deficiency anaemia. "Heavily infected", however, is not a particularly useful concept because the effect of the worms will depend on the iron status and general nutritional status of the host, on the quality and quantity of iron sources in the diet, the absorptive properties of the gut, ulcers, gut lesions, and other infections which may adversely influence iron status. Most importantly, women of reproductive age, especially in developing countries, are invariably experiencing some degree of iron stress through menstruation, pregnancy and lactation, and increased requirements of many nutrients during pregnancy and lactation. This group will be significantly at risk from the effects of the feeding activity of hookworms.

Although it is recognized that hookworm infection has a significant impact on health, the burden is unquantified. There is even less understanding of non-traditional sources of burden, which may be at least as large. For example, iron-deficiency anaemia, one of the commonest manifestations of infection, is a well characterized correlate with impaired cognitive development and compromised educational achievement. There is also no assessment of the long term, potentially inter-generational, consequences for offspring of maternal infection during pregnancy.

2.2 Epidemiology and population biology

The epidemiology and population biology of hookworms has been studied extensively and recently mathematical models have been proposed to explain transmission and identify phases in the host-parasite relationship where available control measures are most likely to be effective. All this work has shown that the overdispersed frequency distribution of numbers of hookworms per host is crucial for maintaining stable populations of the parasites. The common observation worldwide is that, unlike the other main species of soil-transmitted helminth, hookworms are usually acquired gradually during childhood with peak prevalence and intensity values being attained during late teens and early adulthood. These values then will tend to remain steady across all age groups unless successful control interventions are applied. In some areas of high hookworm endemicity, high prevalences are found in children of pre-school age.

Generally, the severity of morbidity is directly related to the size of the worm burden. In the case of hookworms, the amount of blood loss will be expected to increase as the worm burden increases. It is unwise, however, to set a threshold worm burden which will initiate morbidity. The health significance of the burden will also depend on the nutritional and iron status of host.

2.3 Surveys and diagnosis

Surveys to describe the epidemiology of nutritional status have often been carried out much better than those for hookworm infection. Parasitological surveys have to be area specific (nationwide prevalence statistics do not say much) and sometimes seasonal effects must be considered; host age, sex and occupation must be included and samples are best if randomly selected and community orientated. A survey should measure prevalence and intensity and the hookworm species should be identified whenever possible. Without this information, cost effective control strategies are made more difficult to plan and implement. Good surveys must provide for the training needs of the people involved and their supervision. Some teaching/learning aids have been developed for this purpose. (Pawlowski *et al* 1991, WHO 1987, WHO 1994).

3. Biology of hookworm infections in female hosts

Relatively little detail is known about the biology of hookworm infections in female hosts but the prevalence and intensity of hookworm infection are reported to be somewhat lower in females than males. Relationships of this type are almost invariably attributed to presumed behaviour-based differences in exposure to infection. Nevertheless, millions of females of reproductive age are infected with hookworms, many of these harbour hookworms while pregnant when iron needs are high and anaemia is common. Many girls enter puberty and many have their first pregnancy while infected and iron deficient.

Although data for pregnant women are lacking, even seemingly low infections with hookworms adversely influence growth of older children and reduce appetite, physical fitness and cognition (see Figure 5.1). In chronically malnourished populations, light hookworm infections, especially in women with a higher need of iron, should not be overlooked.

Experimental studies with animal hosts and other species of hookworm suggest that natural resistance plays a largely unrecognized, but significant, underlying causal role with regard to these differences. Studies also suggest that the larvae which do not develop in females may be stored as developmentally arrested larvae in the parenteral tissues of their hosts. Reservoir populations of arrested larvae have been demonstrated in the somatic muscles of bitches infected with *Ancylostoma caninum*. Such arrested larvae, presumably after reactivation by hormones associated with lactation, are shed in milk and are infective to suckling puppies. Transmammary transmission probably accounts for about 99% of the hookworms found in neonatal dogs, the remainder being

attributable to transplacental infection. Neonatal hookworm disease caused almost exclusively by *A. duodenale*, is now recognized in suckling human infants. The highly disproportionate occurrence of *A. duodenale* in neonatal children suggests that lactogenic infection, rather than percutaneous infections is the usual basis for neonatal ancylostomiasis. Given that *Necator americanus* is not only present, but often the dominant species in precisely the areas where pure neonatal *A. duodenale* infections are found, it is highly unlikely that human infants acquire *A. duodenale* infection percutaneously by contact with larvae in the environment.

4. Biology of hookworm infections in neonates and infants

Although general patterns in the population biology of hookworms indicate that infections are acquired gradually and do not peak until the age of young adulthood is reached, compelling circumstantial evidence from China indicates that *Ancylostoma duodenale* can pass from the mother, across the placenta, to set up an infection *in utero*. It is not known how this happens; are the larvae those which have just entered the mother and are undergoing a general tissue migration or are they recently activated, arrested larvae?

Hundreds of cases of infantile (<1 year old) hookworm infection and disease (bloody stools, melena, anorexia, listlessness, oedema and vomiting) have been described in China since the 1960s. The mortality rate for this group is from 4-12% due to intestinal haemorrhage or cardiac failure induced by severe anaemia. Hookworm eggs, identified in due course as those of *A. duodenale*, have been found in the faeces of the reported cases. And with the exception of a single worm identified as *N. americanus*, all the adult worms expelled in stools from the infants following chemotherapy or examined at autopsy were *A. duodenale*. Many of the children investigated with hookworm eggs in their stools were neonates (<1 month old). The shortest prepatent period in humans infected percutaneously with *A. duodenale* is about 56 days so it would appear that such children must have been infected before birth while *in utero*. In dogs infected with *A. duodenale* per *os*, the prepatent period can be as short as 22 days.

5. Estimates of the global extent of hookworm infection and anaemia during pregnancy

5.1 Hookworm infections and pregnancy

Recommendations or otherwise about the problem of hookworm-induced anaemia during pregnancy depend on knowledge of the number of such cases. This analysis seeks to offer an order of magnitude estimate of the number of women who are both pregnant and infected with hookworm burdens of a magnitude which is likely to be associated with disease. Among the assumptions made is that a number of spontaneous abortions will occur so that the rate of live births will tend to underestimate the number of women pregnant at any time. The analysis is applied in the first instance to the population of Sub-Saharan Africa.

Fertility data indicate that 24 million women in Sub-Saharan Africa were pregnant at some time during 1990. The estimated prevalence of hookworm infection in this age-group (15-45 years) is 32%, which suggests that some 7.5 to 7.8 million women were both pregnant and infected. The distribution of numbers of hookworms is overdispersed and the number of worms per person is believed to determine the risk of morbidity. Of the 7.5 million pregnant women in Sub-Saharan Africa at risk, approximately a million are estimated to be at risk of clinically demonstrable morbidity if the threshold number is 40 worms. Because of the nonlinear relationship between burden and risk of morbidity the threshold can vary from 50 to 200 worms without changing the population at potential risk of disease by more than some 100,000s.

Although no data exist for the pregnant women group, it has been shown that light infections with hookworm adversely influence growth, even of older children, and also reduce appetite, physical fitness, activity levels and cognition (see Figure 5.1). Therefore even without clincially demonstrated morbidity, infections of <40 worms may have adverse consequences, particularly in chronically malnourished populations in Sub-Saharan Africa, Asia and Latin America.

Total and regional estimates of hookworm infections and pregnancy are shown in Table 5.1. The overall number of women estimated to be both infected and pregnant, using 1990 data, is found to be about 44 million.

Figure 5.1 Potential Nutritional Effects and Functional Consequences of Hookworm Infection in Malnourished Populations

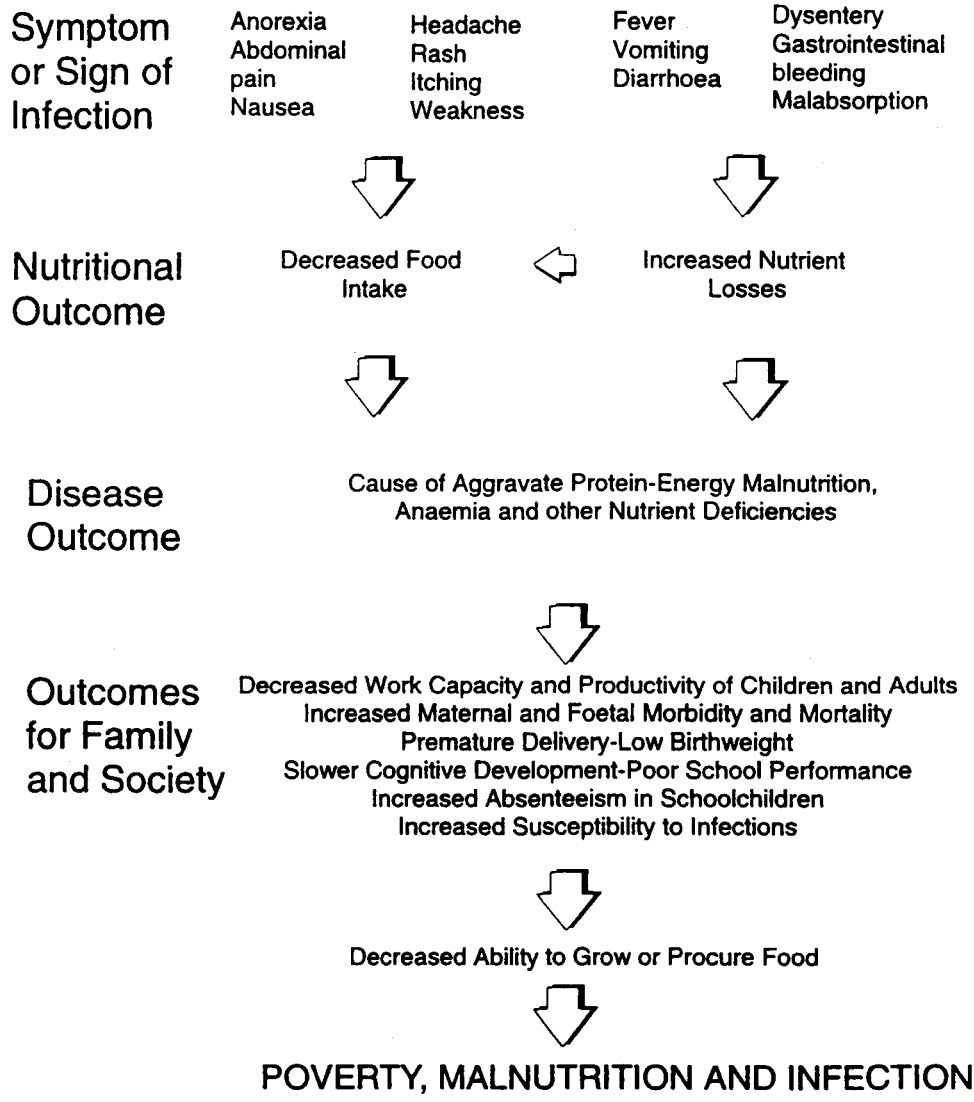

Table 5.1 **Predicted numbers infected with hookworm and at risk of morbidity in different regions of the world (World Bank regions) assuming different threshold worm burdens for morbidity. Fetal mortality is assumed to be 1%. Estimates are given in thousands**

Region	Births	Pregnancies	Infected	>100 Worms	>200 worms
SSA	23320	23553	7537	596	426
LAC	11959	12079	4107	496	327
MEC	13892	14031	3087	171	116
IND	25690	25947	10898	1528	1025
CHN	25065	25316	8607	635	349
OAI	23091	23322	10028	1075	700
total	123017	124247	44264	4502	2944

SSA: Sub Saharan Africa
LAC: Latin America and Caribbean
MEC: Middle Eastern Crescent
IND: India
CHN: Peoples' Republic of China
OAI: Other Asia and Islands

Other simple calculations, based on an earlier year of estimation, suggest that about 30 million pregnant women are currently experiencing hookworm infections, with most of them being due to *N. americanus.*

5.2 Anaemia and pregnancy

For comparison, the estimated numbers of anaemic or iron-deficient persons, the prevalence of anaemia in pregnant women by WHO Region and the classification and severity of the anaemia for pregnant women are given in Tables 5.2 and 5.3.

Table 5.2 **Estimates of the extent of anaemia and iron deficiency in the populations of WHO regions**

WHO REGION	Number of anaemic or iron-deficient persons	Prevalence of anaemia in pregnant women (%)
Africa	206,000,000	52
Latin America	94,000,000	40
Europe	27,000,000	18
Eastern Mediterranean	149,000,000	50
South-East Asia	616,000,000	74
Western Pacific	1,058,000,000	40
Developed countries		18
Developing countries		56
Total	2,150,000,000	51

Adapted from WHO, National strategies for overcoming micronutrient malnutrition. Document A45/3, 1992.

6. Pregnancy in developing countries

Many women in developing countries spend a major part of their lives either in pregnancy or as lactating mothers. These events have a considerable requirement for iron. Each pregnancy requires a transfer of about 300 mg of iron during the third trimester, the mother requires an additional 500 mg of iron to cope with the increased RBC mass needed for a successful pregnancy and each day of lactation involves a transfer from mother to child of about 0.75 mg of iron. A non-pregnant woman of childbearing age will lose about 35 ml of blood (23 - 54 ml) containing approximately 15.5 mg of iron during menstruation. Loss of iron from menstruation is spared during pregnancy and breastfeeding, but the extent of these processes on

iron metabolism is not fully appreciated. For example, it is estimated that some women from sub-Saharan Africa, during the age range from 18-43 years, spend as much as 28% of the time pregnant and 65% lactating; only 7% of this period is likely to be free from these demands on her iron status. In the 25-year period of reproductive activity, such a woman may have had 10 pregnancies and is likely to have experienced considerable periods of iron-deficiency anaemia. During the "free time", menstruation will take its natural toll on iron status. (56% of women of reproductive age in developing countries are judged to be anaemic (Table 5.2)).

Table 5.3 **A classification of the severity of anaemia in relation to public health significance: pregnant women**

Category of Public Health Significance	**Mild-moderate anaemia Hb 70-109 g/l *Hct 0.24-0.329 l/l**	**Severe anaemia Hb < 70 g/l *Hct < 0.24 l/l**
High	> 40%	> 10%
Medium	10 - 39.9%	1.0 - 9.9%
Low	1.0 - 9.9%	0.1 - 0.9%

* Hct = Haematocrit or packed cell volume (PCV), measured as a proportion (red cell volume/blood volume)

From: Report of African Regional Consultation on Control of Anaemia in Pregnancy, WHO/Brazzaville, document AFR/NUT/104, 1989.

Also, in most societies women will be more than mothers, they will be homemakers and agricultural workers, labourers and water carriers. They will be vulnerable to infections with malarial parasites and schistosomes as well as hookworms. The intensity of their hookworm infections, and any effects on their iron status, will depend on their degree of exposure to infective hookworm larvae, exposure being largely determined by cultural traditions and social needs.

In 1989, a WHO Consultation was held in Brazzaville to consider the health issues related to anaemia in pregnancy. The views of this group included the following important information:

Consequences of anaemia in pregnancy

(i) First stage - compensated anaemia; breathless on exertion only.
(ii) Second stage - non-compensated anaemia; breathless at rest.
(iii) Third stage - congestive cardiac failure.

The group concluded that overall, anaemia was found to be responsible for 20% of maternal deaths and contributed to many more deaths. The group stressed that to minimize these effects, special attention is needed to prevent severe anaemia, i.e. those with haemoglobin <70 g/l.

7. Multifactorial aetiology of iron-deficiency anaemia in adolescent girls and women of reproductive age

That iron-deficiency anaemia has a multifactorial aetiology is beyond dispute. It is a complex syndrome and is defined in different ways according to the concerns of health workers and researchers (Appendix: Section 13). In many developing countries females are often poorly nourished and bear a heavy workload. Adequate blood haemoglobin concentrations and balanced iron status are essential for heavy work let alone for the demands of many pregnancies and years of lactation (Section 6). Against these demands, in many societies in developing countries, females are perceived to be of low social value and so physical and emotional neglect may prevail. Girls may be discriminated against in food allocation, deprived of adequate education, expected to marry early in life and to have frequent and numerous pregnancies.

Much evidence shows that the staple diet of millions of women, based on cereals and pulses, does not assure the provision of sufficient dietary iron in a bio-available form for absorption. Other factors in vegetarian diets, such as tannins and phytates, impair iron absorption. Given these nutritional and physiological factors, it is not

surprising to observe that many women of reproductive age experience some degree of iron deficiency anaemia.

Iron-deficiency anaemia is also exacerbated during acute infections with malarial parasites and during chronic infections with hookworms (Section 2), *Schistosoma haematobium* and *Trichuris trichiura*. Evidence from India indicates an association between infections with *Entamoeba histolytica, Giardia intestinalis* and *A. lumbricoides* and the haemoglobin status of the human hosts.

Even though iron deficiency is the most common cause of anaemia in pregnancy world wide, iron deficiency (from nutritional inadequacy, with or without iron loss from intestinal hookworm infections) is not the only cause of anaemia in pregnancy. Resistance to *P. falciparum* malaria is reduced in pregnancy, especially amongst *primigravidae*, and is a frequent cause of anaemia, often profound especially when complicated by folate deficiency, in malaria endemic areas. Folate deficiency as a common cause of anaemia is often profound, where intake does not meet the physiological requirements and the high demands which follow haemolysis from malaria and haemoglobinopathies, and vitamin C, vitamin A, and protein deficiencies can contribute as well. Sickle-cell disease, especially Hb SC disease, is locally important in parts of Africa, and β-thalassaemias minor and intermedia, especially HbEβ-thalassaemias, are locally important in Asia. Since the advent of HIV/AIDS, HIV in Sub-Saharan Africa has been strongly associated with anaemia (often severe) in pregnancy, and with high rates of maternal and infant morbidity and mortality: it is predicted that HIV will have a similar serious impact in Asia.

Although the average intensity of hookworm infection that would initiate the onset of iron-deficiency anaemia is not yet known and will depend not only on the species of hookworm but also the iron status of the subject and other factors, there is no doubt that treatment to remove the infection would relieve the pressure on a pregnant woman's limited iron reserves. Also, measures to reduce the intensity of hookworm infection of adolescent and pre-adolescent girls before pregnancy, especially if continued systematically throughout childhood, would help them to be best prepared for future motherhood.

8. Assessment of anaemia and restoration of iron status

Iron deficiency is one of the commonest nutritional disorders, affecting a large proportion of women of reproductive age in developing countries (Table 5.2 and 5.3). It is safe to assume that iron deficiency is present at a significant level in developing countries as a predominant cause of anaemia or as a major contributory factor in the high prevalence of anaemia. Depleted iron stores indicate the presence of a form of iron deficiency even if anaemia is absent. For this reason, the total proportion of people with some form of iron deficiency is always likely to be greater than those with overt anaemia. It must be noted that anaemia has a multifactorial aetiology (Section 7 and Appendix).

8.1 Testing for iron deficiency and anaemia

There is a range of proven laboratory tests to assess iron status including the measurement of blood haemoglobin concentration, haematocrit, serum ferritin, erythrocyte protophophyrin, serum iron, transferrin saturation and, serum transferrin receptors (WHO/UNICEF/UNU, 1995). However, in many developing countries the application of a range of biochemical tests is limited due to shortage of resources and the fact that high rates of infections and other nutrient deficiencies can interfere with the proper interpretation of most of the tests and thus limit their usefulness. Blood haemoglobin concentration and haematocrit can usually be measured with reasonable reliability and the results can be used to give information about impaired iron status as well as anaemia.

A new portable photometer (HemoCue, AB, Angelhom, Sweden) is now available for measuring blood haemoglobin concentrations in field surveys. It is ideal for this purpose because it is battery-operated, needs no wet reagents, and can be used by (trained) non-laboratory personnel. However, the costs of items such as disposable cuvettes are relatively high in the context of health budgets in developing countries.

8.2 Use of haemoglobin distributions to assess the nature of anaemia and iron deficiency

Anaemia surveys of the maternal and child population are commonly used to assess the iron status of the community because women and young children are the sub-population most vulnerable to iron deficiency. The prevalence of anaemia serves as an index of the severity of iron deficiency. This approach is useful in areas where iron deficiency is the predominant factor responsible for most cases of anaemia, as is often the case in developed countries.

The approach of using haemoglobin distributions to determine the presence or absence of major factors other than iron deficiency is based on the fact that when poor dietary iron intake is the main factor present in the population, as is often the case, it preferentially affects women and children, and has little impact on the haemoglobin level of adult men. Whereas, under other conditions, including other nutrient deficiencies and the increased blood loss due to hookworm, the adult male is not spared. The comparison of an optimal haemoglobin distribution based on a group of individuals who were free from nutrition deficiency or disease with the distribution from a sample under study may very well provide information on whether factors other than poor iron intake are contributing to the high prevalence of anaemia.

Stools can also be investigated to contribute to the assessment of iron status. This is extremely relevant when dealing with hookworm infections. The method measures haem quantitatively (HemoQuant) and its application involving hookworm infection in Pemba Island, Zanzibar, has been made recently by Yip *et al* (Table 8.1) (Schwartz *et al*, 1983).

Table 8.1 **Amount of blood loss estimated by quantitative stool heme analysis for Pemba Island children with different worm loads (Yip *et al*, unpublished)**

Hookworm infection (n = 50 per group)	mean blood loss (ml/day)	SD
Negative	1.24	1.85
Light (1-999 epg*)	1.46	1.07
Moderate (1,000-4,999 epg)	2.96	3.03
Heavy (≥ 5,000 epg)	8.79	7.10

* epg = Eggs per gram of faeces

8.3 Approaches to identifying factors contributing to anaemia

The relative shift of haemoglobin distributions for children, women and men from their respective reference distribution provides valuable information on the cause of the elevated rates of anaemia in women and children: poor iron intake, combined poor iron intake and increased blood loss, or other factors. When there is evidence from a significant shift of men's haemoglobin distribution that causes of anaemia in addition to poor iron intake are present, the best option in defining the other cause or causes is to measure the haemoglobin response to treatment of the suspected conditions(s) with and without iron. Obviously the decision on which therapeutic agent(s) should be used for the trial depends on the existing knowledge of other likely health and nutritional disorders known to exist in the area. In regions where hookworm, malaria or other parasitic diseases are endemic, the use of an anti-malarial or anthelminthic agents can be justified by laboratory documentation of the infection. In areas where other nutrient deficiencies are known to be a common problem, for example folate or vitamin A deficiency, the use of supplements of these nutrients in combination with iron can help diagnose the nature of anaemia for the population. There are two principle reasons for this approach. One is because direct laboratory evaluation of iron status when other nutrient deficiencies

or infectious factors are present is difficult even when detailed laboratory investigation can be performed. The second reason is a feasibility issue. In an area where high rates of severe anaemia are likely to be due to multiple causes, it is often difficult to collect and perform the detailed biochemical tests needed to define micronutrient status and infectious process. However, field haemoglobin measurement and administration of therapeutic agents can be done almost anywhere in the world.

One case example that is helpful to illustrate the use of supplementation or treatment trial to define the nature of anaemia is the recent study of anaemia among pregnant women by Suharno *et al* in Indonesia where vitamin A deficiency is also endemic (Table 8.2). A trial response of anaemia with a combination of iron and vitamin A had a much better response than iron or vitamin A supplement alone, demonstrating that virtually all anaemia can be attributed to vitamin A and iron deficiency.

Table 8.2 **Proportion of anaemic pregnant women responding to supplements and become non-anaemic (Hb $\geq$ 11.0 g/dl)**

Treatment	% Anaemic cases responded (95% CI)
Placebo (N=62)	16% (7 to 29)
Vitamin A only (N=63)	35% (22 to 48)
Iron only (n=63)	60% (54 to 79)
Iron & vitamin A (n=63)	97% (88 to 99)

Source: Suharno D, West C.E., Karyadi D, Hautvast G.A.J. Not only supplementation with iron but also with vitamin A is necessary to combat nutritional anaemia in pregnant women in Java, Indonesia. *Lancet*, 342 : 1325-28, 1993.

8.4 Interventions to restore iron status

It is unlikely that iron deficiency anaemia during pregnancies in the developing world will be prevented by anthelminthic treatment alone or from modification of the usual diet. Iron supplementation or fortification of a dietary vehicle is likely to be needed. Where iron prophylactic programmes can be combined with vitamin A supplementation/fortification, this can be a cost-effective programme for reducing anaemia while safely addressing the vitamin A deficiency as well. Such multinutrient programmes need to adjust dosage to the frequency of contact, e.g. daily or weekly. In areas where vitamin A deficiency is endemic, affecting pregnant and lactating women, as well as children, the effectiveness of deworming coupled with treatment with iron in alleviating anaemia may be weakened unless the vitamin A deficiency is addressed concurrently (Suharno, 1993).

It is not recommended to give high dose vitamin A to pregnant women, rather to provide no more than 10,000 IU daily (approximately 3000 μg). If the chemotherapy based programme (against hookworms and other intestinal helminths) is focused on the immediate post-partum period of infertility (about 4-6 weeks), high dose vitamin A (200,000 IU in a single dose) can be safely given. Results from the field studies completed to date do not suggest that there are *in vivo* interactions between iron and vitamin A at the gut mucosa leading to a loss of effectiveness of one or other of these nutrients. There is no evidence for an adverse interaction between anthelminthic drugs and vitamin A, and it is unlikely that such a problem would occur with concurrent iron supplementation.

A recent study on iron supplementation of anaemic Chinese preschool children has shown that weekly administration of iron tablets both corrected anaemia as effectively as did daily dosing and also drastically reduced intestinal discomfort associated with daily dosing (Liu *et al* 1994). Gastrointestinal complaints are common with daily administration of iron, but they are rare with the weekly dose. Two recent studies in China, one in preschool children (Liu *et al* in press) and the other in pregnant women (Liu *et al* in press) and one in anaemic nonpregnant Indonesian women (Gross *et al*, 1994), have also shown that weekly supplementation can improve haemoglobin levels as much as or more than the standard daily regimen. The generality of this important finding is being examined in studies in pregnant women, adolescent girls and preschoolers in eight countries

in the WHO/UNU/UNICEF study of weekly iron supplements. This weekly effect should significantly increase the coverage, feasibility and value of iron supplementation programmes, particularly in the developing world. It should also make combined anthelminthic chemotherapy and iron supplementation more acceptable, due to a decrease in side affects from daily administration of iron.

Since 1994, about 3 million children of school age (6-15+ years) in Gujarat, India, have been receiving in two dosing rounds per school year, 400 mg Albendazole, 200,000 IU Vitamin A and 60 mg Fe/day. The process evaluation study showed that this programme, which was entirely financed and managed by the Government, was cost effective and stimulated increases of 1-2 g Hb/dl (Gopaldas *et al* unpublished results).

8.5 Predicted impacts, timing and delivery systems of interventions to restore iron status

Possible effects of different interventions on the iron status of anaemic women are estimated in Table 8.3. The important use of this table is to compare the orders of magnitude of potential impact from different strategies. It appears that the potential impact from hookworm control compares favourably with other strategies to improve the iron status of women.

Table 8.3 **Predicted impact from selected interventions to improve the iron status of an anaemic woman**

Intervention	Effect on daily iron balance (mg/day)	Maximal haemoglobin impact (g/dL/month)	Additional iron after one year (mg)
Chemotherapy based hookworm control reduce burden by 40 worms	+ 1.2	0.3	420
Ancylostoma duodenale	+ 0.6	0.2	210
Necator americanus			
Iron supplementation (standard regimens)			
3 mo x 120 mg/d	+ 8.4	2.1	756
3 mo x 60 mg/d	+ 6.0	1.5	540
Dietary modification addition of 50 mg vit. C	+ 1.4	0.3	493
Iron Fortification of Food increase intake by 15 mg/d	+ 1.1	0.3	411
Reproductive pattern prevent one pregnancy	+ 2.1	0.5	588
extend lactational amenses for 6 mo	+ 0.2	0.1	77

The benefits of controlling hookworm infection in women are more diverse than most micronutrient interventions. Hookworm control is an intervention to improve iron status, but is more than that and we do not understand all the ways by which anthelminthic treatment affects the health of children. We are even more ignorant about the effects of anthelminthic treatment on the health of women.

There are three critical times to consider for the intervention to improve or restore iron status in women (Table 8.4). The first is around puberty, in preparation for the years of reproduction and the

greatest economic activity. A unique programme objective is to improve height, but there is no evidence that this occurs. A woman's height is associated with her risk of complications during delivery and her physical capacity for work, apart from iron status. In general, nutrition interventions are believed to have greater potential to affect growth in younger children than in older children. It remains an open question whether deworming during the pubertal growth spurt could lead to greater gain in a girl's height. If this is true, then deworming at this stage in life could yield a height benefit that a girl would carry with her throughout her life. Other benefits such as attenuating the depletion of iron stores or improving weight for height are also important, but less timely in the sense that they could also be achieved at other times.

The second critical intervention time is around reproductive events. This could be further divided into pregnancy, and the post-partum period. Intervention in pregnancy is a most timely way to achieve programme objectives such as infant birth outcomes, and prevention of maternal morbidity and mortality. Anthelminthic chemotherapy at delivery or immediately post-partum would be the ideal time to reduce the vertical transmission of *Ancylostoma duodenale*.

Thirdly, if the programme objective is either to improve work efficiency and the economic productivity of women, or to improve their sense of well-being, quality of life, and caring capacity, then the goal should be to alleviate iron deficiency and the hookworm load of women throughout their adulthood. Where transmission of hookworm is intense, contacting women only once per pregnancy will probably not achieve this goal, especially in societies where family planning is fairly successful. In this case, some way is needed to regularly give anthelminthic treatment to women on, for example, an annual or biannual basis.

Table 8.4 **Possible times to intervene with control of hookworm**

TIME	POTENTIAL OBJECTIVES
Adolescence	Improve pre-pregnancy weight for height Improve pre-pregnancy iron status
Pregnancy and Lactation	**Related to mother** Increase maternal iron stores Reduce maternal death in child birth Reduce hospitalization rates for severe anaemia and haemorrhage Reduce caloric stress in pregnancy and lactation **Related to infant** Improve foetal growth; reduce low birth weight Improve iron stores of infants Prevent vertical transmission of *Ancylostoma* Decrease perinatal mortality Improve early childhood development
Throughout Adult life	Improve economic productivity of women Improve wellbeing and quality of life Improve weight for height of all women Improve iron status in all women

The need to integrate delivery systems for public health interventions has been brought out in many different contexts. Some of the existing delivery systems that could be used to provide anthelminthic chemotherapy to women at these time points are listed in Table 8.5 with examples of countries that now have those delivery systems.

Table 8.5 **Possible delivery systems for control of hookworm in women**

Time	Delivery systems
Adolescence	Secondary schools (Sri Lanka) Women's groups (Indonesia) Ritual initiation groups (Malawi)
Pregnancy and Lactation	Antenatal care (Sri Lanka) Delivery services, TBA kits (Nepal, Bangladesh)
Throughout Adult Life	Community health worker systems (India) Traditional healers (Kenya) Women's groups or cooperatives (Indonesia, Bangladesh) Special women's days (Bangladesh, Nepal) Linkage to existing vertical campaigns, such as iodine, vitamin A, family planning (Indonesia, Nepal) Workplaces, such as cigarette or garment factories, plantations (Indonesia, Sri Lanka)

Points to remember in the choice of delivery systems are: (1) as targeting gets more refined, selection criteria become more complex; (2) as selection criteria get more complex, greater skills and reliability of staff delivering anthelminthics are required; (3) greater skills and reliability require higher levels of training and supervision; (4) higher levels of training and supervision involve greater costs.

Community-based workers in primary health care programmes tend to have too many tasks to perform, to be poorly rewarded, and to be inadequately supported, so great care must be taken in adding delivery of anthelminthics to their workloads and assuming that they have the time and focus to reach most of the intended participants.

9. Anthelminthic treatment

9.1 Drugs

Four anthelminthic drugs, described in the current edition of the W.H.O. Model List of Essential Drugs, may be considered for the treatment of hookworm infection in adolescent girls and women of reproductive age. The drugs, which have been developed by the research-based pharmaceutical industry, are also available as generics from various sources, but they should not be procured without due attention to their quality. Two are substituted benzimidazoles, albendazole and mebendazole; the others are levamisole which is the laevorotatory enantiomer of tetramisole, and pyrantel which is a tetrahydropyrimidine (Table 9.1). All are well-known drugs and hundreds of millions of doses have been used in recent years for the satisfactory treatment of common soil-transmitted helminth infections. There is also extensive experience of their use to treat parasitic infections in farm and domestic animals.

The benzimidazoles in general act as microtubule poisons, binding to the ubiquitous cytoskeletal protein, tubulin. The range of benzimidazole actions extending to adult, tissue and egg stages of parasites gives them a distinct advantage over other compounds in control programmes. In contrast, the action of levamisole and pyrantel against intestinal nematodes is mediated through interference with somatic nicotinic cholinergic transmission.

9.2 Pharmacokinetics in humans

Although there are differences in the individual profiles of the four drugs, all show rapid excretion. Albendazole has a low absolute absorption, it undergoes extensive metabolism in the liver and only the sulphoxide metabolite appears in the plasma at detectable levels. The mean time taken to reach maximum plasma concentration (0.2-0.94 μ g/ml) ranges between 2-2.4 h. The parent compound (albendazole) is active against parasite stages in the gut lumen and the sulphoxide metabolite is active against tissue stages. Mebendazole is poorly absorbed from an oral dose. The fraction that is absorbed is rapidly metabolised and eliminated by the liver.

Table 9.1 Anthelminthic activity of selected drugs in frequent use at the community level[1]

Drugs[2]	Therapeutic activity against[3]				
	Ascaris lumbricoides	*Hookworms (Ancylostoma duodenale and necator americanus)*	*Trichuris trichiura*	*Strongyloides stercoralis*	*Enterobius vermicularis*
Albendazole	4	3	2-3	2-3[4]	4
Levamisole	4	2-3[4]	2	2	2
Mebendazole	4	2-3[5]	2-3[5]	2	3-4
Pyrantel embonate	4	2-3[4]	1	1	3-4

[1] Adapted from - Prevention and control of intestinal parasitic infections. Technical Report Series No. 749. World Health Organization, Geneva. Table 4, p 58.

[2] No attempt has been made to include all the drugs (e.g. flubendazole) or drug combinations used in the treatment of intestinal nematode infections. Listing is strictly alphabetical.

[3] In these estimates of therapeutic activity, the term "cure rate" refers to the proportion of patients treated who are egg-negative on one follow-up examination on a single stool sample. Replicated examinations, repeated samples and more penetrating parasitological methods inevitably produce lower estimates of "cure" than those tabulated. Furthermore, these estimates were derived from the therapeutic literature on trials conducted with drug formulations produced by the original pharmaceutical manufacturers of the compounds. Since the patent protection for many of these compounds has expired in many (but not all) countries, it should be appreciated that many new manufacturers of these drugs exist. Hence in different preparations there may be variations in pharmaceutical formulation, in bioavailability and in therapeutic "equivalence". Rarely is information on these variations available; this would require strictly controlled and probably large-scale clinico-pharmacological trials.

Key: 1 = 0-19% "cure rate" - inseparable from the technical errors associated with the parasitological techniques used in field examinations; 2 = 20-59% "cure rate" - moderate activity; 3 = 60-89% "cure rate" - good activity; 4 = >90% "cure rate" - very good activity.

[4] The higher estimates of "cure rate" are seen after an increased total dose is given, either once or over a period of 2-3 days.

[5] The usual dose of mebendazole is 100 mg, twice daily, for three days, irrespective of age.

Note:

The following single doses are recommended: levamisole, 2.5 mg/kg body weight; mebendazole, 500 or 600 mg; pyrantel, 10 mg/kg body weight (WHO model Prescribing Information, Drugs Used in Parasitic Diseases, 1990). In addition, field practice has shown a single dose of 400 mg albendazole or a single dose of 500 mg mebendazole to be satisfactory (WHO, 1995, *Weekly Epidemiological Record*, 4, 25-28).

Levamisole is rapidly absorbed from the gut and peak plasma levels are reached 1-2 h after a single oral dose. Following extensive metabolism, levamisole is cleared from the body within 48 h. Due to the apparent lack of a suitable analytical procedure, less information has been published about the pharmacokinetics of pyrantel.

9.3 Therapeutic efficacy (Table 9.1)

The popularity of the benzimidazoles is undoubtedly a reflection of their broad spectrum of activity, their excellent tolerance in humans and, in the case of albendazole, the action on adult, larval and egg stages of parasitic helminths.

Albendazole

Of the benzimidazoles, albendazole has the widest range of therapeutic activity and in a single dose is known to be active against the hookworms, *Ancylostoma duodenale* and *Necator americanus.*

Mebendazole

Broadly similar in its range of efficacy to albendazole, it appears to be less effective against hookworm infections in a single dose of 500 mg.. Minor differences exist in its effects on other intestinal helminths.

Levamisole

Its major use lies in the treatment of infections with *Ascaris lumbricoides* and the hookworms. Less effective at a single oral dose than the benzimidazoles in hookworm infections, the merits of the drug may have suffered from the poor design of many clinical trials and the use of coarse techniques of evaluation in hookworm infection.

Pyrantel

Effective against *Ascaris*, the hookworms, *Enterobius* and *Trichostrongylus* spp., its main use is in ascariasis and enterobiasis. In hookworm infections, dosage over 2-3 days has consistently proved superior to single dose regimes.

9.4 Adverse effects

All four drugs are accepted at population level. Minor side effects are seen but are usually transient and are generally well tolerated. It is extremely difficult to assign one all-embracing statistic of incidence of side effects; perhaps 5% would be a reasonable upper limit, but many series produce figures of under 1%. Benzimidazoles when used against intestinal helminths, produce upper gastrointestinal tract symptoms in a small proportion of cases.

Adverse side effects are more commonly associated with the high multiple dose regimes of the benzimidazoles used when treating hydatid disease; the target organs are the liver as evidenced by elevation of hepatic enzymes and the bone marrow, as evidenced by lowered white cell counts. Rises in hepatic enzymes have occurred in 10-15% of treated cases in two recent large series treated with albendazole - (800 mg/day for 28 days, repeated after a 14-day interval for a total of three cycles). Occasional episodes of neutropaenia have occurred during similar high dose regimes, but it is important to stress that all abnormalities are reversible and values rapidly returned to normal on cessation of therapy. In cysticercosis, the pattern of adverse effects differs with headache and other symptoms in the CNS. Such high dose adverse effects seem to be

disease specific. Neither of these adverse effects are usually seen during or after the treatment of intestinal helminthiases.

Levamisole in the low dose regimes employed in intestinal helminth treatment is extremely well tolerated. Agranulocytosis following long term high dose regimes for other diseases is recognised but since medical enthusiasm for this type of treatment has declined, the syndrome has become a rarity. In pyrantel-treated patients, minor gastrointestinal side effects are reported in a very small proportion of cases.

It should be noted that in a few cases erratic migration and/or exit of *Ascaris lumbricoides* through the mouth or nose may occur following treatment with any of these compounds.

9.5 Safety aspects of albendazole and mebendazole benzimidazoles),levamisole and pyrantel in human pregnancy and lactation: a toxological assessment (Table 9.2)

Predictions must be based on animal test results and kinetics in non-pregnant women. Information about genotoxicity is also important because processes causing genetic damage may directly affect foetal and neonatal development. In the case of anthelminthic drugs, little of the necessary primary information is in the public domain, so any evaluation has to be made from reviews and secondary sources. Some of this information is summarized in Table 9.2, largely drawn from the expert opinions of international groups such as JECFA.

Table 9.2 Published Data about Anthelminthic Drugs on the WHO Essential List

Substance*	Relevant Geno-toxicty	Reproduction Toxicity Test Results			Kinetics in Animals			Kinetics in Humans			Regulatory Guidance (a) Humans		
		Seg II	Seg III or multigen	Animals (terato-genicity)	Pregnant	Milk	Non-pregnant	Pregnant	Non-pregnant	Milk	Pregnant	Lactating	Non-pregnant
Albendazole	P 0	P rat + others 0	P 0	P 0	N	N	N	N	P	N	F = A	F = A	U
Levamisole	P 0	P rat + others 0	P 0	P 0	N	N	P	N	C	N	F	F	U
Mebendazole	P	P rat + others 0	P 0	P 0	N	P+	P	N	P	N	A>F	A>F	U
Pyrantel	N	P0 C0	N	P 0	N	P+	P	N	N	P 0	F	F	U

(a) Datasheet advice on major developed countries
F = cautious approval
A = not recommended
U = used

(b) C = full set of results
P = limited results of summary assessment not available
N = no direct statement
+ = positive result
0 = negative result

* Listing is strictly alphabetical.

Albendazole and mebendazole have been shown to have teratogenic effects in some species of laboratory animal, but they have been found not to have these effects in other species including farm animals (in the latter at clinically relevant doses). On balance, it appears that species differences in pharmacokinetics and metabolism afford protection against teratogenic and genotoxic effects in humans during the vulnerable stage in early pregnancy. It is also likely that, as the post-natal development of neonatal animals presumed to be exposed via milk from dosed dams has not been impaired, there is no good experimental data against their use in women who are breastfeeding. These must be seen as tentative opinions.

For levamisole, there are more extensive pharmacokinetic data from non-pregnant animals and humans, and uniform assessments that reproduction and genetic toxicity tests have given negative results. Information about pyrantel is very sparse, but no reports were found of genetic or reproduction toxicity. Formal kinetic studies in animals were also not found, but absorption appears to be very limited.

9.6 General conclusions from the toxicity assessment

Considering the extensive use of all these drugs in animals and humans, the paucity of relevant pharmacokinetic and toxicity data in the open literature is surprising. The nature of the formal assessment by major agencies of the United Nations, and by regulatory bodies for human and animal medicines in a number of western countries, does show that more detailed and extensive experimental and clinical (veterinary and probably human) information is available and has been evaluated.

Nevertheless, necessarily tentative conclusions drawn from the publicly available results suggest that it is probably safe to use selected benzimidazole drugs in women of child-bearing potential, as differences in the doses and in pharmacokinetics and metabolism make it likely that there is little if any risk to pregnant and lactating women or to the breast-fed baby. The size of the margin of protection is uncertain. Levamisole and probably pyrantel are not experimental teratogens or genotoxicants, so these drugs may appear safer to use in women and infants as far as these risks are concerned.

9.7 Drug interactions

The possibility of interactions between any of the four anthelminthic drugs mentioned above and other medicines administered at the same time should be considered, although no interaction appears to have been reported.

9.8 Recent experience from Sri Lanka: anthelminthic treatment of pregnant women

From 56-78% of pregnant women in Sri Lanka have been found to be anaemic and the prevalence of hookworm infection (*N. americanus*) is known from the results of 15 recent surveys to vary from 6 to 89% (mean c.41%).

Given the wide distribution of hookworm infection and high prevalence of iron-deficiency anaemia in pregnant women, many of whom have poor dietary resources, it made sense in Sri Lanka to treat all pregnant mothers with an anthelminthic drug on the presumption that hookworm infection is a likely contributory cause. This approach is further strengthened by the recent observation by Atukorala *et al* (1994) that a single course of mebendazole given after the first trimester of pregnancy in addition to iron-folate supplements resulted not only in a marked increase in haemoglobin concentration but also in a significant improvement in iron status. Thus the anthelminthic treatment was followed by improvements in the beneficial effects of iron-folate supplements. Currently mebendazole 100 mg bd for 3 days is used, but this is shortly to be replaced with a single dose of mebendazole 500 mg to ensure better compliance.

10. Research Topics

1. Investigate the relative contribution of hookworm and other parasitic infections to iron-deficiency anaemia in girls and in women of child-bearing age in various ecological and cultural settings.

2. Study the influence of nutritional deficiencies (e.g. iron, folate and vitamin A) and infections (e.g. malarial parasites and hookworms) on iron status, vitamin A status, growth and pelvic development of girls before and during pregnancy.

3. Investigate the relative merits of daily and weekly iron supplementation during pregnancy, in association with deworming in various environments.

4. Incorporate into the system now in operation in Sri Lanka, procedures and codes of practice to permit evaluation of safety and effectiveness of the programme.

5. Follow the birth outcomes of women who either received or did not receive anthelminthic treatment after the first trimester of pregnancy.

6. Investigate if lactation performance improves with the control of hookworm infection and iron nutritional status of pregnant and lactating mothers.

7. Study user perceptions of the health effects of hookworm infection and of the consequences of its treatment in pregnancy.

8. Investigate whether pregnancy or lactation modifies the host-parasite relationship in hookworm infection.

9. Investigate the transplacental and transmammary routes of *A. duodenale* infection.

11. Recommendations

1. Since hookworm infections contribute to iron-deficiency anaemia, it is recommended that, in areas where these infections are endemic (prevalence > 20-30%) and where anaemia is prevalent, hookworm control using one of the following four drugs: albendazole, levamisole, mebendazole and pyrantel, be included in strategies designed to improve the health, development and nutritional status of girls and women.

Single-dose, oral anthelminthic treatment can also be given to pregnant and lactating women. However, as a general rule, no drug should be given in the first trimester.

2. The results of experimental studies and of observations in women and men on the toxicity, pharmacokinetics and metabolism of albendazole, levamisole, mebendazole and pyrantel should be published as an aid to better understanding of their safety-in-use in public health medicine. Pharmaco-vigilance observations especially in women should be considered in order to demonstrate their safety in the clinical use of these medicines.

3. Strategies for hookworm control during pregnancy should be linked to other PHC contact points with pregnant women where iron and other micronutrient needs are concurrently addressed.

4. Primary health care initiatives involving chemotherapy should be planned and implemented as part of comprehensive programmes for the control and prevention of iron deficiency anaemia in reproduction: such programmes should include water supply, environmental sanitation, malaria and schistosomiasis control, iron folate supplementation, health education and family planning, according to locally-defined epidemiological needs.

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13. Appendix on anaemia and iron deficiency Anaemia

Anaemia is recognized by detection of a reduced haemoglobin concentration based on age and sex variables (Table 13.1). Common causes of anaemia are iron deficiency (including that due to hookworm), malaria, and hereditary defects of red cell or haemoglobin production. Relative or absolute nutritional deficiencies of folic acid, vitamin C and vitamin A may also contribute to the development of anaemia.

It is well known that normal haemoglobin distributions vary with age, sex, and at different stages of pregnancy (Table 13.1). In addition a number of factors such a altitude and smoking can cause significant shift of haemoglobin distributions (CDC, 1989). There is also evidence that individuals of African extraction in the USA have Hb values 5 to 10 g/l lower than those of European extraction, and that this is not related to iron nutrition (Perry *et al* 1991). Proper interpretation of Hb or Hct values requires the application of appropriate cutoffs and modulating factors. The WHO criteria for concentrations of haemoglobin and haematocrit corresponding to anaemia are shown in Table 13.1.

Table 13.1 **Haemoglobin and haematocrit (PCV) concentration below which anaemia is present (WHO/UNICEF/UNU, 1995)**

Age/sex group	Haemoglobin below*		Haematocrit (1/1) below*
	g/l	mmol/l	
Children under 5 years	110	6.83	0.33
Children 6-14 years	120	7.45	0.36
Non-pregnant women	120	7.45	0.36
Pregnant women	110	6.83	0.33
men	130	8.07	0.40

* Respectively, 10 g/l, 0.62 mmol/l or 0.03 l/l lower, in populations of predominantly African extraction. See Table VI.1 (WHO/UNICEF/UNU, 1995)

In addition, a previous consultation defined severe anaemia in pregnancy as Hb< 70 g/l and very severe anaemia with risk for congestive heart failure as Hb <40 g/l. More detailed anaemia criteria for various age groups across childhood, adolescent, and pregnancy as well as adjustment factors for altitude and smoking, have been developed by CDC/Atlanta.

Iron deficiency

Iron deficiency is considered to be the insufficient iron supply for the optimal physiological production and function of iron dependent cellular components. Iron deficiency state is usually recognized by specific biochemical tests to measure variables such as transferrin saturation and serum ferritin. Anaemia is a consequence of more severe form of iron deficiency due to impaired haemoglobin production.

Iron deficiency anaemia

Anaemia caused by inadequate iron supply for haemoglobin production.

Hookworm anaemia

A form of iron deficiency anaemia related to poor iron status due to increased gastrointestinal blood loss caused by the feeding activity of intestinal hookworms.

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