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Controlling human Oesophagostomiasis in Northern Ghana

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-Chapter 9-

General discussion

General Discussion

Ever since the inception of research into human oesophagostomiasis in northern Ghana and Togo just over two decades ago, *Oesophagostomum* infection has been shown to be common and to cause significant health problems in that part of the world. Our knowledge concerning *Oesophagostomum* infections and associated morbidity was limited. In a regional meeting organised in the Ghanaian northern city of Tamale in 1998, it was decided to embark on a research project to identify suitable means through which infection and morbidity control could be achieved. This was expected not to be an easy job since we did not even know how transmission took place and why infection was particularly common in this area and absent elsewhere. The logical steps were to follow the recommended lines of control as used in other soil-transmitted helminth infections: repeated mass treatment as described by for instance Albonico and co-workers (Albonico *et al.*, 1999).

Two main problems were expected to arise from such approach: rapid re-infection from the vast animal reservoir of *Oesophagostomum* infections in non-human primates and the development of resistance against albendazole as seen in veterinary use. In fact both of these hesitations have been countered over the course of time. First, simultaneous molecular and epidemiological research conducted by de Gruijter and co-workers demonstrated that the human and the simian parasites are different and that human infection with infective larvae from the simian host is unlikely to take place (de Gruijter *et al.*, 2004). Secondly, albendazole is increasingly being used at a population level for control in other helminth infections. Millions of doses of albendazole have been distributed in programmes to control soil-transmitted helminths infections and lymphatic filariasis and so far there are no serious indications of development of resistance. Nonetheless, we must be prepared that one day such resistance might develop. The risks to see resistance develop in *Oesophagostomum* infections, however, is particularly small for two reasons: the efficacy of treatment in *Oesophagostomum* infections is much greater than in other helminths infections so the reservoir of *Oesophagostomum* worms surviving treatment is much smaller than in those other infections, and less treatments appear to be necessary. The data shown suggests that the reservoir of remaining infections is too small, after a number of treatments, to allow continued transmission.

An additional important notion to be considered before exploring the possibilities of control was how the impact of treatment was to be monitored. Monitoring can not be made on the basis of generally accepted procedures of stool examination because of the inability to differentiate *Oesophagostomum* eggs from those of hookworms. Instead stool cultures had to be used but there is hardly any reliable precedent to use that technique for parasitological follow up studies. Moreover, mere levels of infection are inappropriate parameter to justify control of morbidity. Recent experience with abdominal ultrasonography to visualize *Oesophagostomum*-induced pathology paved the way to evaluate the impact of mass treatment not only on the basis of infection but also on morbidity (Storey *et al.*, 2001a).

Eventually, we did embark on a systematic albendazole-based intervention programme, and the results obtained were compared with those in a control area. The conclusions drawn from this study are reported in this thesis and bridge some of the gaps in our current knowledge and understanding of the transmission biology of human *Oesophagostomum* infections. New ideas and information concerning the transmission and morbidity patterns and the possibility of control have been reported in the preceding section and are now being discussed.

The study design and diagnosis

Our longitudinal study design was based on repeated cross-sectional surveys, in a rural part of northern Ghana. We choose a rather big, seemingly homogeneous area to serve as the treatment area (“intervention area”). This area was fairly well demarcated to the east by the Ghana-Togo border, to the south by the Gambaga escarpment and to the west by the major road that links Bawku and Nakpanduri, the two biggest towns in the area. A set of neighbouring villages was selected to serve as a control area, which was supposed to be similar to the intervention area in many respects. However, in due course of time, it appeared it was not. The prevalence of *Oesophagostomum* infections was significantly lower in the control area than in the intervention area although hookworm prevalences and tribal-, professional-, religious- and age- structure were all very similar. This was an unpleasant consequence of our lack of understanding of the factors determining transmission and distribution of infection.

Several factors influenced the choice of this area as the study area. First of all, the prevalence of *Oesophagostomum* infection was earlier found to be very high in this focus compared to other areas of the *Oesophagostomum* endemic zone (Yelifari *et al.*, 2005). Secondly, the rural nature of the area was expected to limit movement of the inhabitants in and out of the area and therefore makes the area particularly suitable for the purpose of mass drug distribution and subsequent monitoring of the impact of treatment.

Reliable recovery for examination and treatment of individual inhabitants of the study area was based on a detailed census of the area involving some 20,000 people carried out under GPS guidance because no documented census data was available. Regular updating of the database was similarly essential. Each round of mass treatment included the inhabitants of the intervention area only. For ethical reasons individuals in the control areas, who were shown to harbour either *Oesophagostomum* or hookworm infections, were treated as well. During subsequent samplings in the longitudinal study we decided to examine new subjects, originally not examined (and in the control area: not treated) before. In the last survey, it was planned to not only examine a new group of subjects in the control area, but also to re-examine those treated one or two years before, to establish the rate of re-infection over time in individuals who were treated and still living in the population that was not treated as a whole. Due to a misunderstanding, both the control and the intervention area were covered by a round of albendazole-ivermectin mass treatment administered by the Lymphatic Filariasis Elimination Program. As a result, the control area wasn't a proper control area any more and the project was thus redirected towards an operational pilot control programme. This change of aims was justified thanks to the very great and rapid impact of the treatments in the intervention area (see chapters 5-7). Further analysis and follow up over the next few years is now a joint activity of the *Oesophagostomum* Intervention Research Project and the Lymphatic Filariasis Elimination Program.

Analysis of infection was complicated by the fact that the well established Kato method cannot be used to differentiate between *Oesophagostomum* and hookworm infections. So we had to rely on stool cultures, the interpretation of which is far less established. The disadvantage of the compulsory choice was that comparison with the results of other studies is difficult, even when focusing on the impact of intervention on hookworm alone. To overcome this disadvantage, Kato smears

were examined along with the stool cultures. Using both of these methods together showed that stool cultures had not only the advantage to enable differentiation between *Oesophagostomum* and hookworm but also to provide us with a much more sensitive diagnostic tool for monitoring the evolution of hookworm infections. Comparing Kato results with those of coproculture prior to intervention, when most infections were heavy, the sensitivity of both methods was quite similar, but after a number of rounds of mass treatment the sensitivity of Kato was shown to be very much inferior to that of stool culture. It means that in hookworm control programs, monitoring on the basis of Kato only produces over-optimistic results.

Abdominal ultrasound investigation was carried out to measure the occurrence of *Oesophagostomum*-induced nodular lesions both at baseline and following mass treatment to assess the morbidity of infections and the impact of treatment on morbidity. The ultrasonographic studies revealed that in 52.5% of infected subjects (parasitological methods) no lesions were ultrasonically detectable. Similarly, in 23.3% of subjects who were parasitologically negative, ultrasonically visible lesions, considered to be specific *Oesophagostomum*-induced were detected. These observations are a reflection of the lack of sensitivity of both coproculture and ultrasound diagnostic tools. This underlines the complementarity of both methods and the benefits of a combined use of both tools, in this research.

Infection and transmission of *Oesophagostomum* and hookworm

Before mass treatments were carried out, baseline prevalences and intensities of *Oesophagostomum* and hookworm infections in the area were determined and the possible associations between both helminth infections and certain demographic and environmental factors were explored. The baseline patterns of *Oesophagostomum* and hookworm distributions and transmission, reported upon in chapter 2, confirm earlier observations in northern Ghana and in northern Togo. Adult females carry much of the *Oesophagostomum* infection in the area, an observation consistent with previous findings (Polderman *et al.*, 1991; Krepel *et al.*, 1992; Pit *et al.*, 1999a and Yelifari *et al.*, 2005). Even within the seemingly homogeneous intervention area, the *Oesophagostomum* infection rates varied a lot from one village to another: some clusters of villages were significantly more infected than others. The reasons for this clustering effect are still not well

understood. Religion, wealth, family size or the presence of animals did not offer an explanation to the clustering seen. Geographical/geological factors need to be studied in more detail. Geographical and tribal clustering was previously described in endemic villages with the Bimoba tribe mostly implicated to be the most vulnerable tribe (Polderman *et al*, 1991; Krepel *et al.*, 1992; Pit *et al.*, 1999a and Yelifari *et al.*, 2005). Our current data showed that over 98% of the inhabitants who live in the highly infested *Oesophagostomum*-villages belong to the Bimoba tribe. This does not imply, however that there is a causal relationship between being infected and being a Bimoba. In the few villages with a truly mixed population, Bimoba and Kusasi were equally infected. The predominance of the Bimoba tribe in the high-prevalence villages is more likely to be related to the historical pattern of migration of the tribes of the area. In spite of our lack of understanding details of the epidemiology, clustering and distribution of infection prior to intervention, the reduction in prevalence and intensity of infection was shown to be very impressive everywhere in the treatment area.

With regard to hookworm, prevalence and intensity of infection were more homogeneous in the area as a whole and geographical clustering was less pronounced. The prevalences of both nematodes among the 171 young children, of 3 years and below, examined before mass treatment was administered were impressively high. Over 27% of these children were infected with *Oesophagostomum* and 55.7% with hookworm, which points to the fact that transmission of both nematodes is quite intense in this area. This further justifies the need for control.

Patterns of morbidity

Since it was not at all sure that any lasting reduction of infection could be achieved with repeated mass treatment, reduction of morbidity was the logical second objective of this study. The relationship between infection and the degree of pathology, however, was not well understood either. Infection, as measured with stool culture procedures, reflects the presence of egg-producing adults and ultrasound positivity reflects the presence of immature juveniles that apparently fail to develop into adults. In earlier studies Storey and co-workers discussed the relationship between positivity in coproculture and ultrasound and they concluded that both might exclude each other: the development of nodules could indicate the

inability of the developing worms to grow into adults; in those patients stool culture was thought to remain negative (Storey *et al.*, 2001d). This hypothesis was supported by the frequent observation of clinical patients with negative coprocultures and of subjects with positive coprocultures without signs of disease. The hypothesis, however, requires further study.

The observations described in chapter 3 of this study did not confirm Storey's hypothesis. In fact a close correlation could be shown between the presence and number of ultrasonically detectable lesions and the intensity of infection in terms of infection rates and larval counts. The consequence of these observations is that reduction of transmission and infection is bound to be reflected in reduction of pathological lesions as well.

Treatment and impact of treatment

Periodic anthelmintic chemotherapy together with efforts aimed at promoting good hygiene is the key intervention in current intestinal nematodes control strategies (e.g. Albonico *et al.*, 1999). From recent information about recommended drugs for helminth infections, albendazole, alongside with levamisole, mebendazole and pyrantel are considered potentially useful drugs (WHO, 1997). In our study, repeated mass drug distribution was carried out using a single dose of 400 mg of albendazole and resulted in the treatment of about 70% to 79% of the population in the intervention area. The choice of albendazole is based on results of previous drug trials conducted using albendazole, levamisole, mebendazole and pyrantel against asymptomatic *Oesophagostomum* infections in which albendazole proved to be the most effective drug (Krepel *et al.*, 1993). Albendazole is shown to be effective against many helminths infections including hookworm, *Ascaris lumbricoides* (Rossignol *et al.*, 1983; Coulaud *et al.*, 1984), *Strongyloides stercoralis* (Mbendi *et al.*, 1985), *Trichuris trichiura* (Mbendi *et al.*, 1985), *Enterobius vermicularis* (Coulaud *et al.*, 1984; Mbendi *et al.*, 1985), *Hymenolepis nana* and *Echinococcus granulosus*. Albendazole is also part of the ivermectin-albendazole combination therapy currently being used in the Global Lymphatic Filariasis Elimination Programme. Albendazole acts by selective binding to nematodes tubulin, inhibits tubulin polymerase activity to prevent the formation of microtubules and eventually stop cell division (Lacey *et al.*, 1990). Consequently, it has both larvicidal and ovicidal effects on nematodes (Borgers and

Nollin, 1975; Lacey *et al.*, 1987; Van Den Bossche *et al.*, 1982; Maisonneuve *et al.*, 1985).

The results of the remarkable impact of repeated mass treatment with 400 mg of albendazole have been measured at short-term (3 weeks after treatment; reported in chapter 5) and at long-term (one year, two years and three years after treatment; reported in chapters 6, 7 and 8). The impact of treatment was evaluated in comparison with baseline levels of infections in the treatment area (before mass treatment was carried out) and with the changes in the levels of infections in the control area. The treatment impact was also assessed simultaneously for both *Oesophagostomum* and hookworm infections. Parasitological cure rates measured 3-4 weeks after a single 400 mg dose of albendazole treatment was 98.8% for *Oesophagostomum* and 75% for hookworm. For hookworm the cure rate was 79% and comparable to what has been reported in the literature, when based on Kato smear examination (this thesis, chapter 5 and Bennett and Guyatt, 2000). When based on coproculture, the cure rate was only 51%.

The infection rates of *Oesophagostomum* decreased dramatically one and two years after repeated mass treatment as compared with the pre-intervention level of infection. The data suggest some reinfection took place in the first year. Such reinfection was thought to be related to the importation of infection from outside the treatment area but the study design did not allow us to solidly prove this. Only one year after the first round of mass treatment, the impact on signs of pathology was almost as great: the rate of nodular pathology decreased from 38.2% to 6.2% in the intervention area but remained the same in the control area. These data suggest not only that no or few new nodules were formed in that year but also that the existing nodules disappeared rapidly. Similar findings on the short life span of tissue dwelling larval stages have been reported previously on a much smaller scale (Storey *et al.*, 2001c).

It is relevant to note that the infection rate of *Oesophagostomum* continued to go down even after mass treatment was interrupted. In hookworm infections, on the other hand, the coproculture-based prevalence went down from 86.9% to 36.9% after one year, and to 23% after two years of mass treatment. After interruption of mass treatments, however, the prevalence increased again to 31.5%.

Overall, it can now be concluded that repeated mass treatment with albendazole is effective in controlling *Oesophagostomum* transmission and associated

morbidity. This conclusion is in sharp contrast to the findings of Djemila Pit, in Togo, who described that very rapid re-infection took place after albendazole treatment (Pit *et al.*, 2000b). The explanation is probably that in Pit's experiments only selected individuals were treated while in the present study a great effort was made to treat as closely as possible the entire population. In Pit's study a large reservoir of infection remained, in the present study the reservoir of infective eggs and larvae was –apparently- effectively removed. Even an old *Oesophagostomum*-infected man, who refused treatment and who has been followed parasitologically did not seem to be able to re-infect others living in his house (Unpublished observations).

It can be concluded that transmission seems to be interruptible in the case of *Oesophagostomum* but not in hookworm. What could be the explanations for the difference?

Several factors are likely to play a role. First, *Oesophagostomum* would seem to have an ill adapted parasite human host-relationship (the parasite is essentially a parasite of non-human primates and apparently underwent a change to be transmissible to humans. The very high efficacy of albendazole will certainly be of crucial importance in explaining the success in *Oesophagostomum* control. A third factor is likely to be in the comparatively small size of the infested area. The very limited area of endemicity enabled us to cover the entire transmission area with albendazole, reducing the risk of importation of infection from non-treated areas. Finally, it is possible that the route of infection, through ingestion of infective L₃-larvae complicates effective transmission and facilitates control. On the other hand, the route of infection could not be determined with certainty so this explanation remains rather hypothetical.

Much of the research on control of human oesophagostomiasis as described in the present thesis is based on interventions in a carefully followed (field-) research setting. Evaluation of the impact of albendazole-ivermectin treatments as performed in the framework of the Lymphatic Filariasis Elimination Program in the total area of North Ghana showed that even in a setting of a nation-wide operational intervention program, . elimination of human oesophagostomiasis may be possible. .

Conclusions and Recommendations

1. This study has demonstrated that effective control of infection, of transmission and of pathology in *Oesophagostomum* infections is possible.
2. The data suggests that in spite of the locally very high prevalence of infection prior to intervention, elimination of human oesophagostomiasis is within reach.
3. Experience showed that the albendazole-ivermectin based programme towards elimination of lymphatic filariasis has a much broader impact than on filariasis and well recognized helminth infections only. Close collaboration between different disease control activities needs to be stressed.
4. To ascertain successful completion of the intervention activities, an extension of treatment is essential to cover all *Oesophagostomum*-endemic areas of Northern Togo, also those areas where lymphatic filariasis is considered to be absent, and where currently no albendazole-ivermectin treatment is given.
5. Additional careful monitoring over the next few years, and a final follow-up investigation after a couple of years is needed. When no infections are found any more, repetition of such survey a few years later should be carried out. Indeed, due attention is required in this maintenance phase of the elimination of human oesophagostomiasis.