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Controlling human Oesophagostomiasis in Northern Ghana

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-Chapter 7-

Mass treatment with albendazole reduces the prevalence and severity of *Oesophagostomum*-induced nodular pathology in northern Ghana

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Abstract

Previous surveys conducted in northern Ghana where *Oesophagostomum bifurcum* is endemic showed that *O. bifurcum*-induced nodular pathology could be detected in up to 50% of the inhabitants. The impact of albendazole-based mass treatment to control both infection and morbidity is assessed and compared with the situation in a control area where no mass treatment has taken place. A significant reduction in the prevalence of infection based on stool cultures was achieved following two rounds of mass treatment in one year: from 52.6% (361/686) pre treatment to 5.2% (22/421) 1 year later (χ_1^2 = 210.1; $P < 0.001$). At the same time, the morbidity marker of ultrasound-detectable nodules declined from 38.2% to 6.2% (χ_1^2 = 138.1; $P < 0.001$). There was a shift from multinodular pathology, often seen in heavy infections, to uninodular lesions. In the control villages where no treatment took place, *O. bifurcum* infection increased from 17.8% (43/242) to 32.2% (39/121) ((χ_1^2 = 9.6; $P < 0.001$). Nodular pathology decreased slightly from 21.5% to 19.0%, but a higher proportion of these subjects developed multinodular pathology compared with baseline ((χ_1^2 = 5.5, $P = 0.019$). It is concluded that repeated albendazole treatment significantly reduces *O. bifurcum*-induced morbidity.

Introduction

In a number of villages in northern Ghana where *Oesophagostomum bifurcum* is endemic, abdominal ultrasound has demonstrated that up to 50% of subjects have *O. bifurcum*-induced nodular pathology (Storey *et al*., 2001b). Most of the affected persons develop subclinical oesophagostomiasis, whilst approximately 2% progress to clinical oesophagostomiasis and may eventually require surgical intervention if untreated (Storey *et al*., 2001b). Two distinct types of nodular disease due to *O. bifurcum* infection have been described in this area. In multinodular disease, characterised by the presence of hundreds of pea-sized nodules in the colon wall, the patient presents with non-specific symptoms of general abdominal pain, persistent diarrhoea and weight loss. Uninodular disease, called 'Dapaong tumour', on the other hand, has typical signs of an abdominal mass and is sometimes, but not always, associated with localised abdominal pain and fever (Haaf and van Soest, 1964; Storey *et al*., 2000a).

Albendazole is considered one of the drugs of choice against a variety of soil-transmitted nematodes and is easy to use as a single 400 mg oral dose (Montresor *et al*., 1998; Urbani and Albonico, 2003). Albendazole is also the drug of choice for the treatment of *O. bifurcum* infection and *O. bifurcum*-induced nodular pathology and has been shown to reduce the prevalence, number, size and lifespan of the ultrasound-detectable nodules (Storey *et al*., 2001d).

Because of the high prevalence of human oesophagostomiasis in northern Ghana and Togo as well as the severity of clinical symptoms in some infected subjects, control efforts are now being implemented in the region. Control is based on mass treatment with albendazole and results have mainly been monitored in terms of reductions in the parasite load with the aim of transmission control. A major objective of control, however, is to reduce morbidity. The present study focuses on the impact of repeated mass treatment on the marker for morbidity, the ultrasound-detectable abdominal nodules. Disappearance of the nodules and changes in the appearance of the visible nodules are followed along with the changes in parasitological markers of infection, i.e. the presence and numbers of third-stage (L3) *O. bifurcum* larvae in stool cultures.

Patients and methods

Study area and subject selection

Before the study was started, 29 villages and 1227 compounds in an *O. bifurcum*-endemic area of northern Ghana were mapped with a global positioning system (GPS 12; Garmin International Inc., Olathe, KS, USA) and approximately 17,500 subjects who live in the area were registered and assigned unique identification numbers, as civil registries are absent in the area. The research area (Figure 1.8, page 13) was split into two: an intervention area where two rounds of mass treatment were given; and a control area where only infected individuals were treated for ethical reasons but no mass treatment took place. The population densities of the intervention area and the control area were similar.

In both areas, stool samples were examined from approximately 10% of the population. One to three weeks later, those persons were visited again and examined by ultrasound if they were present. Follow-up surveys were performed in September 2002, at which time 5% of the total population were examined. The persons included in the baseline and the follow-up surveys were randomly chosen from the total population and nobody was included twice. Most of the subjects in the 2002 survey in the intervention area had been treated twice, some once and others not at all (Figure 1.10, page 20-21). In the control area, none of the subjects examined in 2002 had received treatment the year before.

Clinical and parasitological investigations

The procedures for surveillance, stool collection and coproculture were similar to those reported previously (Ziem *et al*., 2005a).

Briefly, a 6 g subsample from each stool sample was mixed with an equal volume of vermiculite; the mixture was then divided into three equal 2 g portions and cultured for 5-7 days in three Petri dishes. Coprocultures were performed to differentiate the third-stage larvae of *O. bifurcum* from those of hookworm since the eggs cannot be differentiated morphologically. The characteristic third-stage larvae of *O. bifurcum* were distinguished from those of hookworm and *Strongyloides* spp. according to the procedure used by Blotkamp *et al*. (1993). Results were based on the larval counts of the first and second culture, with the third culture serving as a backup in case a culture was spoiled due to gross contamination with maggots or fungi.

All those for whom stool culture results were available were also invited to attend a mobile field clinic for ultrasound examination. A portable ultrasound machine (Kretztechnik AG, Tiefenbach, Austria) equipped with a 3.5-4.5 MHz convex array transducer and powered by a generator was used to scan the abdomen with the patient in the supine position. Detection of ultrasound-detectable nodules was performed according to the procedure described by Storey *et al*. (2001d) and nodular pathology was classified according to the criteria used by Ziem *et al*. (2005a).

Shortly after the baseline survey, the eligible population in the intervention area was offered treatment with a single 400 mg oral dose of albendazole (Zentel®; GlaxoSmithKline, Mayenne, France). Local nurses were assisted by trained field workers during the directly supervised drug administration. Children aged 3 years and below were exempted from treatment. A key element in the mass treatment was that the mobile treatment teams kept a careful record for each of the 13,612 individuals registered in the area, as well as of newcomers since registration. The time of the surveys, the number of persons examined and the mass treatment coverage are summarised in Figure 1.10 (page 20-21)..

Data analysis

Oesophagostomum bifurcum infection and ultrasound-detectable nodular lesions were expressed as prevalence figures stratified by age group. Three types of ultrasound findings were recognised: no pathological lesion, uninodular pathology (only one nodule detected) and multinodular pathology (more than one nodule detected either in clusters or in different locations along the colon wall). *Oesophagostomum bifurcum* infection was also presented as prevalence figures stratified by intensity class expressed as the proportion of subjects with ‘heavy infection’ (larval count >100 larvae in two cultures), ‘moderate infection’ (larval count 33-100 larvae in two cultures), ‘light infection’ (larval count <33 larvae in two cultures) and ‘no infection’ (no larvae in two cultures).

Differences in the prevalence of nodular pathology and *O. bifurcum* infection between the treated and non-treated groups at baseline and 12 months after treatment were analysed using (χ^2 and non-parametric tests (Kruskal-Wallis) for comparison between groups. Changes in the frequencies of nodular lesions between treated and non-treated groups were also tested on pre- and post-treatment scores for each lesion type. A P-value of <0.05 was used to imply statistical significance for all tests.

Ethical considerations

During all surveys and mass treatments, the villagers were informed about the purpose of the project and their consent to participation was obtained. The Ghana Health Services Ethics Committee in Bolgatanga approved the strategies and objectives of the study. The project was also approved by the Danish Central Scientific-Ethical Committee.

Results

The numbers of subjects examined in the surveys and the number who received treatment during both rounds of mass treatment in the intervention area are presented in Figure 1.10 (page 20-21). At baseline in September 2001, 686 subjects from the intervention group and subjects from the control group were examined by coproculture and abdominal ultrasound. Twelve months later in September 2002, the follow-up survey involved 421 subjects in the intervention group and 121 subjects in the control group. During mass treatment, 78.4% and 81.9% of all subjects in the intervention area received treatment in the first and second treatment round, respectively.

At baseline, the prevalence of *O. bifurcum* infection as determined by coproculture was significantly higher in the intervention area compared with the control area (52.6% vs. 17.8%; (χ_1^2 = 88.4; $P < 0.001$). On ultrasound examination, significantly more *O. bifurcum*-induced anechogenic nodular lesions were detected in the intervention group than the control group (38.2% vs. 21.5%, (χ_1^2 =22.3; $P < 0.001$) (Table 7.1). Among those with nodular pathology, the distribution of multinodular and uninodular pathology was also different between groups. In the intervention group, 159 of 262 (60.7%) of the ultrasound-positive subjects showed multinodular pathology.

The association between the intensity of *O. bifurcum* infection and nodular pathology at the individual level is presented in Table 7.2. At baseline, in the intervention area the proportion of subjects with nodular pathology increases with increasing larval count. In the control area, although only light infections were

Table 7.1 Prevalence of *Oesophagostomum bifurcum* infection as determined by coproculture and types of *O. bifurcum*-induced nodular pathology as determined by abdominal ultrasound before intervention and after two rounds of mass treatment

	Intervention area		Control area	
	No. of subjects	%	No. of subjects	%
Pre intervention (September 2001)				
No. examined	686	242		
O. bifurcum positive	361	52.6[*,†]	43	17.8[*]
Nodular pathology	262	38.2[*,†]	52	21.5[*,†]
Uninodular pathology [a]	103	39.3	41	78.8
Multinodular pathology [a]	159	60.7	11	21.2
Following two rounds of mass treatment (September 2002)				
No. examined	421	121		
O. bifurcum positive	22	5.2[*,†]	39	32.2[*,†]
Nodular pathology	26	6.2[*,†]	23	19.0[*]
Uninodular pathology [a]	16	61.5	12	52.2
Multinodular pathology [a]	10	38.5	11	47.8

[a] Percentages are of those with positive nodular pathology.
[*] Intervention area compared with control area, $P < 0.05$.
[†] Baseline compared with follow-up, $P < 0.05$.

detected, the proportion of subjects with nodular pathology was significantly higher among those infected than those without infections. Similar trends were observed in the follow-up survey, indicating that the risk of developing nodular pathology is higher among those who excrete large number of eggs (Table 7.2).

Nodular pathology and treatment

The evolution of culture positivity and nodular pathology in the villages in the control area as well as in the intervention area following two rounds of mass treatment are presented in Table 7.1. The infection rate was reduced from 52.6% to 5.2% (($\chi_1^2 = 210.1$, $P < 0.001$) in the intervention area, whilst the fraction of nodule positivity declined to a lesser extent, from 38.2% to 6.2% ($\chi_1^2 = 138.1$; $P < 0.001$). After treatment, only one person excreting more than 100 L_3-larvae was found; no nodules were seen in that person. In the control villages where no treatment took place, *O. bifurcum* infection significantly increased from 17.8% to 32.2% (($\chi_1^2 = 9.6$, $P = 0.001$), although nodular pathology decreased from 21.5% to 19.0%. Among the 421 subjects in the intervention group examined at the follow-up survey, 284 persons had received both treatments and 11 (3.9%) of them were infected with *O. bifurcum*. In 19 (6.7%) persons, nodular pathology was seen on ultrasound examination. Among the 54 subjects who received only one of the treatments, 3 (5.6%) and 5 (9.3%) subjects had *O. bifurcum* infection and nodular pathology, respectively. Among the 83 subjects who were not treated at all, 14 were new immigrants who came into the area after treatment had been completed and 69 were children ≤3 years of age. *Oesophagostomum bifurcum* infection and nodular pathology were highest among these immigrants: four (28.6%) were infected and two (14.3%) were ultrasound positive. Although four (5.8%) of the children were infected, none of them had nodular pathology (data not shown).

Discussion

Two rounds of mass treatment with a 400 mg single dose of albendazole were administered to a population in an *O. bifurcum*-endemic region in northern Ghana. The treatments were given shortly after the rainy season and just before the onset of the next rainy season. Along with a strong reduction in the proportion of subjects excreting *O. bifurcum* eggs, the prevalence, severity and appearance of ultrasound-detectable nodular pathology changed dramatically over 12 months.

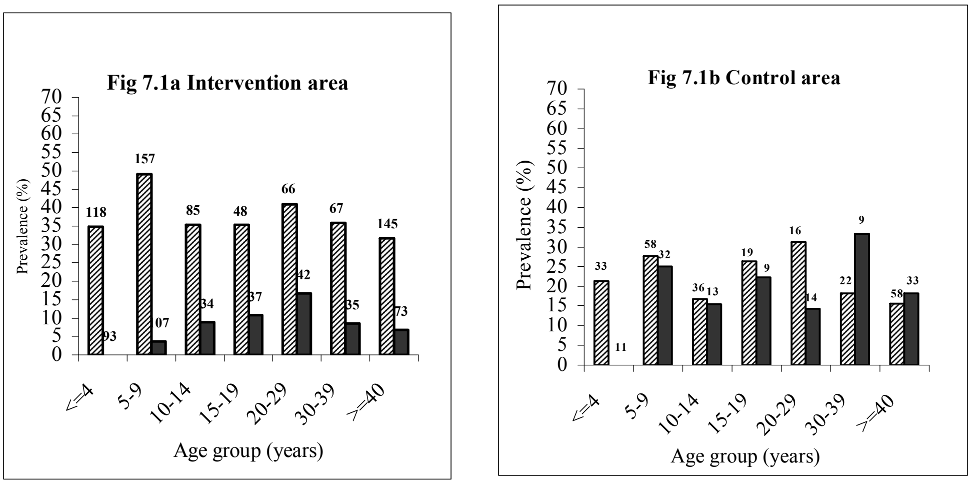
Figure 7.2 shows that the disappearance of nodular pathology is more pronounced in young children than in adults. This can possibly be explained by assuming that the reversibility of ultrasound-detectable nodular pathology is slower in adults after treatment owing to possible scarring around the nodules.

Table 7.2 Presence of nodular pathology as determined by abdominal ultrasound in relation to the presence and number of larvae in coproculture at baseline and at 12 months after treatment in the intervention area and the control area.

	All	Coproculture results [a]				
		All positive	Light infection	Moderate infection	Heavy infection	Neg.
Intervention area						
Stool examination Pre-intervention	686	361	263	63	35	325
Positive for nodular pathology [b]	262 (38.2)	179 (49.6)	119 (45.2)	34 (54.0)	26 (74.3)	83 (25.5)
Stool examination 1 year post intervention	421	22	20	1	1	399
Positive for nodular pathology [b]	26 (6.2)	4 (18.2)	3 (15.0)	1 (*)	0 (*)	22 (5.5)
Control area						
Stool examination Pre-intervention	242	43	43	0	0	199
Positive for nodular pathology [b]	52 (21.5)	13 (30.2)	13 (30.2)	0 (*)	0 (*)	39 (19.6)
Stool examination 1 year post intervention	121	39	32	7	0	82
Positive for nodular pathology [b]	23 (19.0)	14 (35.9)	11 (34.4)	3 (42.9)	0 (*)	9 (11.0)

[a] Light infection: larval count >0 to <33; moderate infection: larval count 33-100; heavy infection: larval count >100.
[b] The figures in parentheses refer to the percentages of subjects (N) with ultrasound-detectable nodules in that particular class of infection intensity as determined by stool culture.
[*] No percentage was calculated when N<5.

Figure 7.1: Prevalence of nodular pathology by age at baseline and 12 months following treatment in the intervention area.



Following two rounds of mass treatment, a 90% reduction in the *O. bifurcum* infection rate was achieved in the intervention group and, at the same time, ultrasound-visible nodular pathology was also reduced, although slightly less (~84%). This is to be expected since changes in pathological processes are likely to lag behind the disappearance of the parasite itself. Moreover, it has been shown that albendazole is more effective in killing the lumen-dwelling adult worm than the larvae that are 'protected' in nodular lesions (Storey *et al.*, 2001a). In fact, it is quite surprising that this type of pathology is normalised so quickly. In schistosomiasis for example, a significant reduction in egg excretion is easily achieved, but reversal of ultrasound-proven periportal fibrosis may take much longer (Mohamed-Ali *et al.*, 1991) even when higher doses of praziquantel are used. In the non-treated group where no mass treatment took place, the prevalence of infection increased over the year of follow-up and pathology remained unchanged. This implies that the reduction in nodular pathology achieved in the intervention area must be due to the mass treatment and is unlikely to be due to year-to-year variation as has previously been described (Storey *et al.*, 2001a).

Nodular pathology is more frequent and more severe in subjects with heavy infection than in those with light infection. After two rounds of mass treatment, larval counts declined dramatically, leaving the population with only a small number of light infections. Parallel to this change in parasitological parameters, morbidity expressed as the prevalence of ultrasound-detectable colonic lesions was reduced in a similar, although slightly slower manner. A simultaneous shift was seen from multinodular to uninodular pathology.

It can be concluded that repeated albendazole treatment is highly effective in reducing *O. bifurcum*-induced morbidity.

Conflicts of interest statement

The authors have no conflicts of interest concerning the work reported in this paper.

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