Two-year follow-up of *Schistosoma mansoni* infection and morbidity after treatment with different regimens of oxamniquine and praziquantel

B. Gryseels* and **L. Nkulikyinka** *Project Bilharziose, Coopération Belgo-Burundaise, Bujumbura, Burundi*

Abstract

Three study groups in the Rusizi plain (Burundi) were examined parasitologically (duplicate 28 mg Kato slides) and clinically (history, abdominal palpation) 0, 1·5, 3, 6, 12 and 24 months after treatment for *Schistosoma mansoni* infection. Infected subjects in Maramvya (n=430) were treated randomly with oxamniquine 20, 30 or 40 mg/kg; those in Bulinga (n=457) with praziquantel, 20, 30 or 40 mg/kg; those in Bulamata (n=333) with praziquantel, 30 or 40 mg/kg. In children (<20 years) in Maramvya and Bulamata, infection rates and intensities returned almost to pretreatment levels one to 2 years after treatment. In Bulinga, reinfection in children was much less intense. Hardly any reinfection occurred in adults in Bulinga and Maramvya; in Bulamata, half of the cured adults were reinfected, most of them lightly, 2 years after treatment. The initial parasitological advantage of the higher dosages of both drugs disappeared generally 3–12 months after treatment. There was no indication of predisposition to heavy reinfection after treatment of subjects with initial high egg counts. Little relation between pre-treatment egg count and morbidity was observed. The impact of chemotherapy on hepatomegaly was limited and observed only in adults treated with 40 mg/kg of either drug. Spleen rates in children and adults were not affected. Abdominal pain was reduced in almost all treatment groups for 3 to 24 months. The frequency of bloody diarrhoea decreased dramatically in children and adults from all 3 villages. This effect lasted 24 months in Maramvya, 12 months in Bulinga and 6 months in Bulamata, and was not dose-dependent. It is concluded that: (i) repeated population chemotherapy combined with sanitation is necessary to achieve lasting impact on infection rates; (ii) retreatment intervals should be adapted to age group and, possibly, local endemicity levels; (iii) the morbidity impact of population chemotherapy in these conditions was greater on intestinal than on hepatosplenic disease; (iv) lower, cheaper treatment schedules may in the long term be as effective as those with high cure rates.

Introduction

Although population-oriented chemotherapy is now widely accepted as a major tool in the control of schistosomiasis, only a few studies have concentrated on its long term efficacy, particularly as concerns reinfection in endemic areas and actual reduction of morbidity. In this study we have followed for 2 years 3 study groups in the Rusizi plain (Burundi), submitted to therapeutic trials for *Schistosoma mansoni* infection with oxamniquine and praziquantel at different dosages. The short term results of these trials have been published earlier (GRYSEELS *et al.*, 1987). The study villages were not uniform concerning pretreatment prevalences and intensities and therefore, presumably, transmission; therefore, the data from each village will be presented separately.

Population and Methods

The study took place in 3 villages in the south of the Rusizi plain, Burundi, between September 1983 and April 1986. The region has been described in detail elsewhere, including the geographical and epidemiological baseline data of the areas and villages concerned (GRYSEELS & NKULIKYINKA, 1988). Maramvya, where oxamniquine at 20, 30 or 40 mg per kg body weight was tested, is a village in a mixed cotton and rice culture area. Bulinga (praziquantel, 20, 30 or 40 mg/kg) is a marshy cotton culture *paysannat*. Bulamata (praziquantel, 30 or 40 mg/kg) is a rice culture village.

After an initial screening of the population by duplicate 28 mg Kato slides, in which compliance exceeded 85%, all individuals excreting eggs of *S. mansoni* (except those with contra-indications) were treated with one of the randomly allotted schedules. In none of the 3 villages were specific measures for the reduction of transmission undertaken during the study. The therapeutic procedures, dates of treatment, pretreatment prevalences and intensities of infection, and the composition of the treatment groups, described in detail elsewhere (GRYSEELS *et al.*, 1987), are summarized in Table 1. There is no specific transmission season in the Rusizi plain to which optimal periods for treatment could be linked (GRYSEELS, 1985).

The treated individuals were examined before treatment, and then 6 weeks, 3, 6, 12 and 24 months after treatment. At each survey, the patients were submitted to a stool examination (duplicate 28 mg Kato slides from a single stool sample), a standardized questionnaire in Kirundi concerning his or her current health problems, and abdominal palpation in supine position. Hepatomegaly was measured under the costal arch and considered significant if it extended 2 cm or more; splenomegaly was measured as described by HACKETT (1944).

The microscopists were submitted to inter- and intra-observer quality control, in which 15 to 20% of the slides were re-examined, with satisfactory results. All medical histories and examinations were performed by the same, experienced nurse (L.N.), under supervision and regular control from a physician (B.G.).

Mean egg loads were calculated as geometric means of the number of eggs per gram of faeces (epg) of individuals excreting eggs. Because of the sensitivity

*Affiliated with the Institute for Tropical Medicine of Antwerp. Present address for correspondence and reprints: Laboratory for Parasitology, Faculty of Medicine, University of Leiden, P.B. 9605, 2300 RC Leiden, The Netherlands.

of this measure to missing values, particularly if few people are infected (as is the case after treatment), only those who attended all surveys were included in the calculation. The significance of differences of proportions was tested with one-tailed z-scores.

Results

Most subjects attended all follow-up sessions, and most others missed only once or twice (Table 1); the participation rate in Maramvya was lower than in the other villages, but was still satisfactory. The percentages of subjects excreting *S. mansoni* eggs, and of those with heavy infections (>100 epg), and the mean egg loads at the successive surveys are shown respectively in children (<20 years) and adults (≥20 years), per village and treatment group, in Figs 1–3.

In Maramvya, children were rapidly reinfected in the first 12 months after treatment (Fig. 1). The overall negativity rate (in all 3 dosage groups) diminished from 65% just after treatment to 35% one year after. The initial advantage in children of the oxamniquine 40 mg regimen over the 30 mg regimen vanished after 3 to 6 months; the 20 mg regimen remained inferior until one year after treatment (Fig. 1a). In the second year of follow-up, little reinfection appeared to take place: the overall negativity rate at 2 years was still 35%, with no significant difference between the treatment groups.

The overall frequency of heavy infections in children, which had been reduced from 75% to 8% six weeks after treatment, increased to 42% one year after treatment. The initial inferiority of the 20 mg regimen in this respect had by then disappeared, as is shown in Fig. 1b. In the second year after treatment, these percentages underwent little further change.

The mean egg load in positive children dropped from an overall value of 346 epg to 46 epg after treatment; one year later, it had increased to 190 epg, with almost equal levels for the different treatment groups (Fig. 1c). No significant increase occurred in the second year of follow-up.

In adults in Maramvya, the overall negativity rate of 93% at 6 weeks diminished to 79% in 2 years. The initial result with 20 mg/kg was inferior but, due to reinfection, the negativity rates of all 3 groups were practically equal 2 years after treatment (Fig. 1a).

The overall frequency of heavy infections in adults decreased from 46% to 0·5% after treatment, and was only 3% 2 years after treatment, with no difference between the respective dosage groups (Fig. 1b). The mean egg loads of positive individuals remained also at minimal levels throughout the whole follow-up period in all 3 groups (Fig. 1c).

In Bulinga, the overall negativity rate of 64% at 6

Table 1. Number of people examined, treated and re-examined in the different villages and treatment groups

	No. examined	No. positive	No. treated	Number examined[a] Co1	Co2	Co3	Co4	Co5	No. examined 6 times
Maramvya (oxamniquine, September 1983)									
<20 years									
20 mg			61	57	56	49	41	53	30
30 mg			47	42	46	41	39	41	29
40 mg			55	49	51	42	38	42	25
Total	271	175	163	148	153	132	118	136	84
≥20 years									
20 mg			109	95	102	86	83	98	62
30 mg			82	76	77	62	67	66	39
40 mg[b]			76	67	65	62	55	60	38
Total	436	290	267	237	244	210	205	224	139
Total	707	465	430	386	397	342	313	360	223
Bulinga (praziquantel, November 1983)									
<20 years									
20 mg			110	109	100	109	101	99	86
30 mg			94	93	91	94	91	91	85
40 mg			95	94	87	92	84	79	69
Total	767	318	299	296	278	295	276	269	260
≥20 years									
20 mg			62	61	54	58	59	55	46
30 mg			48	48	40	46	44	41	33
40 mg			43	42	32	37	38	36	26
Total	542	186	153	151	126	141	141	132	105
Total	1309	504	457	453	410	442	423	407	345
Bulamata (praziquantel, April 1984)									
<20 years									
30 mg			106	104	98	94	92	90	81
40 mg			87	81	83	76	76	77	64
Total	463	206	193	185	181	170	168	167	145
≥20 years									
30 mg			69	65	66	61	51	53	39
40 mg			56	54	54	51	50	48	44
Total	355	137	125	119	120	112	101	101	83
Total	818	343	333	319	316	297	284	283	228

[a]Co1=Control 1 (6 weeks), Co2=Control 2 (3 months), etc.
[b]Split dose; about 15 people who did not come for their second dose were classified in the 20 mg/kg group.

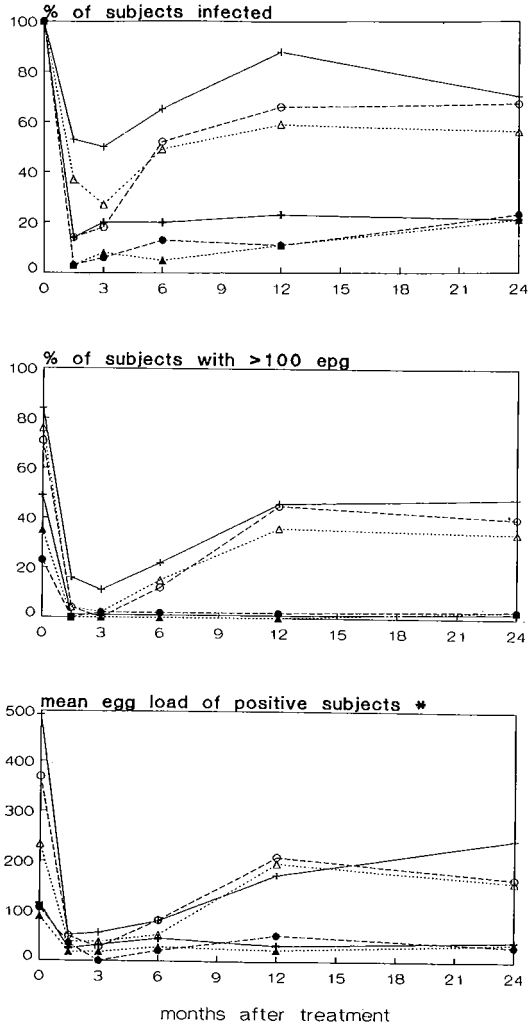

Fig. 1. Reinfection in Maramvya (oxamniquine). Symbols used in Figs 1–3: subjects below 20 years, 20 mg —+—; 30 mg ---△---; 40 mg—○—; subjects 20 years or over, 20 mg —+—; 30 mg ---▲---; 40 mg —●—. *Mean egg loads of only those subjects attending all surveys.

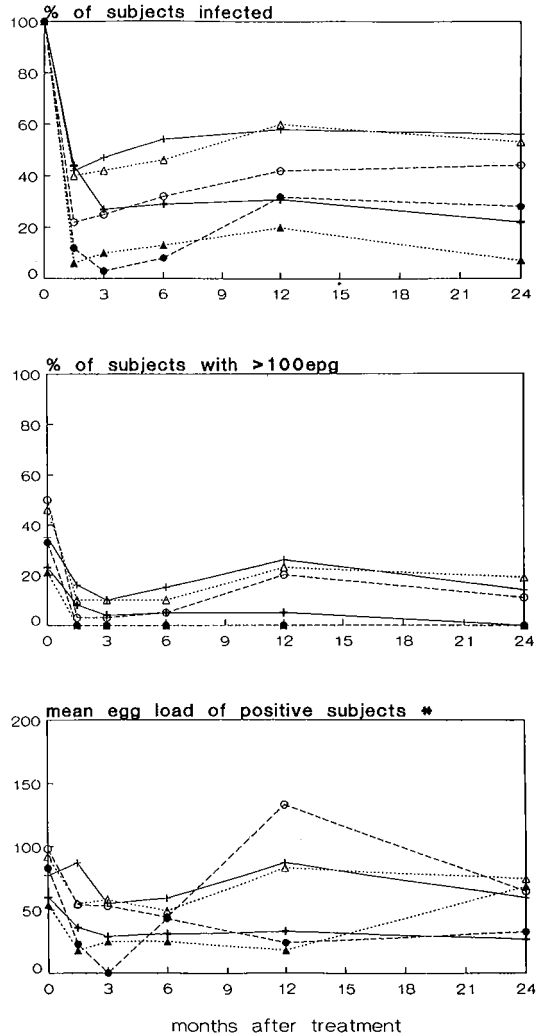

Fig. 2. Reinfection in Bulinga (praziquantel). Symbols as in Fig. 1.

weeks in children decreased to 48% 2 years after treatment. Although initially only the 40 mg regimen gave satisfactory cure rates, the negativity rates of the 3 treatment groups were not statistically different 2 years after treatment (Fig. 2a). The overall frequency of heavy infections in children dropped from 43% to 10% 6 weeks after treatment, increased to 23% one year after treatment, and fell again to 15% after the second year. The scores for this quantity were initially dose-dependent, but these differences vanished during the follow-up period (Fig. 2b). The mean egg load of positive individuals was low before treatment (overall, 88 epg), fell to 55 epg 3 months after treatment, and increased to 93 epg one year after treatment (66 epg after the second year), again with no relation to dosage from the 3rd month onwards (Fig. 2c).

In adults, the initial overall negativity rate of 84% diminished to 72% one year after treatment, and improved again to 81% one year later. The 20 mg regimen was less effective than the others just after treatment, but one and 2 years later its results were as good as those of 40 mg (Fig. 2a). The overall frequency of heavy infections fell from 25% before treatment to 2% 3 months after it. The frequency was still 2% one year after treatment, and 0% 2 years after treatment, with no difference between the dosage groups (Fig. 2b). The mean egg loads were very low before treatment (overall, 63 epg); they diminished to, and remained at, minimal levels of 20–30 epg in all groups (Fig. 2c).

In Bulamata, reinfection in children was very considerable. The overall negativity rate of 72% 6 weeks after treatment decreased to 21% one year after treatment, and 16% one year later. The initial advantage of the 40 mg regimen had disappeared after one year (Fig. 3a). The frequency of heavy infections fell from 55% to 6%, but increased to 38%

after one year and to 49% after two; there was no difference between the 2 treatment groups (Fig. 3b). The overall mean egg load fell from 141 epg before treatment to 54 epg after 6 weeks, and rose to 147 epg 2 years later, with no difference between the two groups (Fig. 3c).

In adults, a slower but steady reinfection took place. The initial overall negativity rate of 87% decreased to 50% in 2 years; the advantage of the 40 mg regimen over that of 30 mg was maintained throughout the follow-up period (Fig. 3a). The frequency of heavy infections, which had fallen from 42% to 4% overall, was 6% after one year, and 12% 2 years after treatment, with no significant difference between the 2 treatment groups (Fig. 3b). The mean egg loads fell from 80 epg to 50 epg 6 weeks after treatment and did not increase thereafter in either group (Fig. 3c).

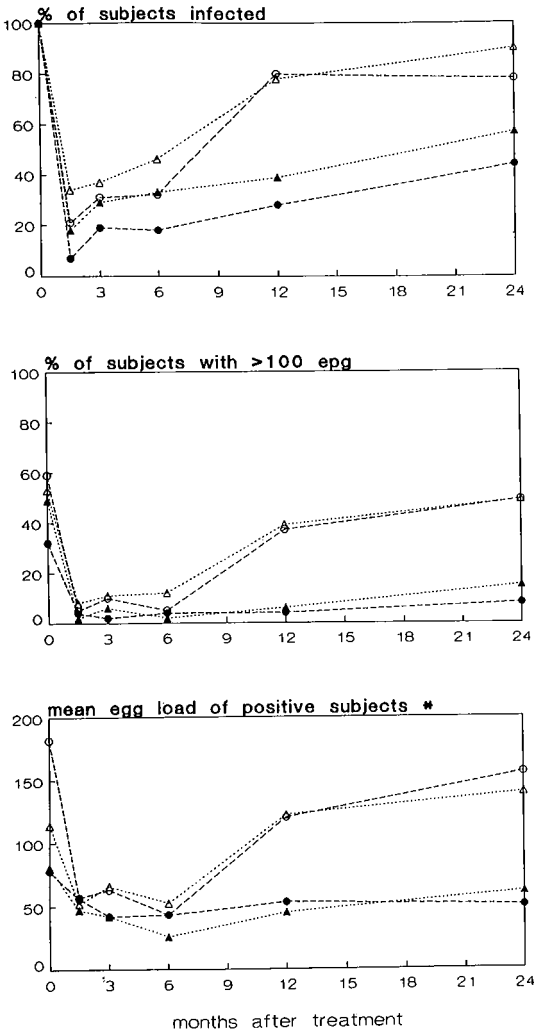

Fig. 3. Reinfection in Bulamata (praziquantel). Symbols as in Fig. 1.

Table 2 shows that the frequency of heavy infections, 2 years after treatment, was not significantly higher in children who had heavy infections before treatment than in those who had less intense infections. Thus, there was no indication of predisposition to heavy (re-)infection in children with high initial egg counts. The analysis is shown only for children who received optimal treatment, that is 40 mg of either drug, in order to avoid bias from treatment failures. Reinfection in adults was too low to allow an analogous analysis.

Morbidity

In Table 3, the respective frequencies of relevant symptoms are shown, before treatment, per age group and village, for those excreting fewer and more than 100 epg, respectively. A significant difference was observed only for hepatomegaly in adults in Bulinga, and for bloody diarrhoea in children in the same village. Further analysis with more detailed egg output groups, or quantitative measures of organomegaly, did not lead to different results. Intense hepatomegaly was infrequent: only 9 people (4 in Bulinga, 5 in Maramvya) had a liver extending more than 4 cm under the costal arch; 6 of them were excreting more than 100 epg. Spleens rating more than Hackett scale 3 were seen in 93 cases (43 in Bulinga, 34 in Maramvya, 16 in Bulamata); 34 of the patients were excreting more than 100 epg.

The impact of treatment on morbidity is shown in Tables 4–8. Hepatomegaly (Table 4) decreased significantly, though not dramatically, in adults in Maramvya and Bulinga treated with 40 mg/kg of oxamniquine or praziquantel, respectively. This effect took place 3 to 12 months after treatment. Splenomegaly (Table 5) was reduced significantly only in children in Maramvya treated with oxamniquine 20 mg/kg. No significant decreases were further observed for either frequency or intensity of organomegaly in any village, age or treatment group.

Six weeks after treatment, the frequency of abdominal pain (Table 6) was significantly reduced in all age and treatment groups in Maramvya. This decrease

Table 2. Frequency of heavy infections 24 months after treatment according to pretreatment egg loads in children treated with 40 mg praziquantel or oxamniquine

Eggs per gram before treatment	Maramvya (oxamniquine)	Bulinga (praziquantel)	Bulamata (praziquantel)	Total
1–100	2/11 (18%)	0/39 (0%)	6/27 (22%)	8/77 (10%)
101–350	1/11 (9%)	1/28 (4%)	7/28 (25%)	9/67 (13%)
>350	4/20 (20%)	1/12 (8%)	5/22 (23%)	10/54 (18%)
Total	7/42 (17%)	2/79 (3%)	18/77 (23%)	27/198 (14%)

$\chi^2=1{\cdot}79$, $0{\cdot}25<P<0{\cdot}5$ (not significant).

Table 3. Relation between egg output and morbidity before treatment

	Age (years)	epg[a]	No.	Frequency (%) of HM	SM	AP	D	BD[a]
Maramvya	<20							
		≤100	40	52	58	68	20	57
		>100	122	50	57	81	14	35
	≥20	≤100	142	24	23	90	9	23
		>100	122	18	26	92	9	26
Bulinga	<20	≤100	168	26	39	83	23	14
		>100	129	29	29	85	16	27*
	≥20	≤100	114	18	23	90	13	20
		>100	37	35*	24	89	8	24
Bulamata	<20	≤100	86	27	33	65	7	19
		>100	105	34	31	85	8	23
	≥20	≤100	72	11	17	78	3	8
		>100	53	13	15	81	10	11

[a]HM=hepatomegaly; SM=splenomegaly; AP=abdominal pain; D=diarrhoea; BD=bloody diarrhoea; epg=eggs per gram of faeces.
*Significant difference ($P<0{\cdot}05$).

Table 4. Percentage frequency of hepatomegaly before and after treatment

Group	0	Time after treatment 6 weeks	3 months	6 months	12 months	24 months
Maramvya						
Under 20 years						
20 mg	52	57	53	53	47	54
30 mg	40	55	48	47	49	41
40 mg	58	63	62	53	67	59
20 years or over						
20 mg	19	20	20	17	21	22
30 mg	19	21	21	25	15	25
40 mg	28	20	16*	16*	17*	18
Bulinga						
Under 20 years						
20 mg	23	29	28	28	28	24
30 mg	27	26	28	29	28	27
40 mg	32	33	27	27	21	15
20 years or over						
20 mg	21	28	26	21	20	16
30 mg	19	28	23	27	26	17
40 mg	26	15	14*	17	14*	17
Bulamata						
Under 20 years						
30 mg	34	25	26	30	34	42
40 mg	28	31	31	34	30	43
20 years or over						
30 mg	6	5	3	5	13	8
40 mg	16	19	14	18	21	25

*Significant ($P<0{\cdot}05$) reduction compared to pretreatment value.

remained significant up to 24 months after treatment in most groups. In Bulinga the frequency of abdominal pain showed a significant decrease in all groups, 1·5 to 3 months after treatment. 6 months after treatment, the effect remained only in adults treated with praziquantel 30 or 40 mg/kg; in the latter group, it lasted 2 years. In Bulamata, a transitory (1·5 to 3 months) decrease was observed, but not in children treated with 30 mg/kg. The frequency of simple diarrhoea (Table 7) was significantly, but very temporarily, reduced in children treated with oxamniquine 30 mg/kg, and in children in Bulinga treated with praziquantel 20 and 40 mg/kg. The frequency of bloody diarrhoea (Table 8) was dramatically reduced

in all treatment groups in the 3 villages; the intensity of the effect was not dose-dependent. The decrease lasted 2 years in Maramvya, 12 to 24 months in Bulinga and 6 months in Bulamata.

In Fig. 4, these results are summarized for all villages and treatment groups. As a whole, it is clear that the impact of the treatment on hepatomegaly and splenomegaly was minimal if not non-existent. The

Table 5. Percentage frequency of splenomegaly before and after treatment

Group	0	Time after treatment 6 weeks	3 months	6 months	12 months	24 months
Maramvya						
Under 20 years						
20 mg	63	50*	47*	42*	69	48
30 mg	48	50	51	42	55	32
40 mg	56	55	54	47	74	51
20 years or over						
20 mg	23	24	25	23	34	15
30 mg	31	30	31	33	34	28
40 mg	20	17	16	13	11	20
Bulinga						
Under 20 years						
20 mg	40	42	47	40	42	36
30 mg	33	44	41	39	40	35
40 mg	30	36	33	37	47	31
20 years or over						
20 mg	21	23	15	21	24	16
30 mg	19	33	25	31	28	20
40 mg	31	24	28	29	22	18
Bulamata						
Under 20 years						
30 mg	34	41	53	56	49	43
40 mg	30	34	51	53	45	37
20 years or over						
30 mg	9	13	17	22	29	18
40 mg	21	24	23	31	23	27

*Significant ($P<0{\cdot}05$) reduction compared to pretreatment value.

Table 6. Percentage frequency of abdominal pain before and after treatment

Group	0	Time after treatment 6 weeks	3 months	6 months	12 months	24 months
Maramvya						
Under 20 years						
20 mg	85	53*	64*	71*	71*	66*
30 mg	89	43*	61*	71*	64*	46*
40 mg	78	45*	61*	67	68	62
20 years or over						
20 mg	92	63*	73*	80*	76*	56*
30 mg	93	64*	66*	79*	74*	71*
40 mg	87	58*	69*	73*	67*	63*
Bulinga						
Under 20 years						
20 mg	80	78	72*	83	85	80
30 mg	87	75*	77*	86	88	77*
40 mg	85	68*	68*	85	81	68*
20 years or over						
20 mg	87	75*	80	78	92	69*
30 mg	94	81*	83*	78*	86	80*
40 mg	91	79*	75*	76*	61*	67*
Bulamata						
Under 20 years						
30 mg	80	73	77	78	89	83
40 mg	80	68*	71*	80	84	84
20 years or over						
30 mg	80	68*	64*	70*	76	70*
40 mg	79	67*	63*	76	82	91

*Significant ($P<0{\cdot}05$) reduction compared to pretreatment value.

Table 7. Percentage frequency of simple diarrhoea before and after treatment

Group	0	Time after treatment 6 weeks	3 months	6 months	12 months	24 months
Maramvya						
Under 20 years						
20 mg	16	14	20	10	15	13
30 mg	19	0*	10	12	15	2
40 mg	11	8	16	10	16	7
20 years or over						
20 mg	8	5	9	7	4	15
30 mg	10	19	4	8	2	8
40 mg	9	7	8	5	4	0*
Bulinga						
Under 20 years						
20 mg	25	11*	9*	17	18	15
30 mg	18	15	13	16	20	22
40 mg	17	3*	10	11	20	19
20 years or over						
20 mg	13	11	7	3	14	7
30 mg	15	10	8	15	27	20
40 mg	9	2	11	11	8	8
Bulamata						
Under 20 years						
30 mg	8	9	17	13	25	21
40 mg	8	6	19	17	33	18
20 years or over						
30 mg	6	5	8	0	14	11
40 mg	5	4	2	6	14	8

*Significant ($P<0{\cdot}05$) reduction compared to pretreatment value.

Table 8. Percentage frequency of bloody diarrhoea before and after treatment

Group	0	Time after treatment 6 weeks	3 months	6 months	12 months	24 months
Maramvya						
Under 20 years						
20 mg	43	12*	11*	13*	10*	24*
30 mg	36	5*	9*	7*	3*	7*
40 mg	44	14*	8*	10*	11*	21*
20 years or over						
20 mg	24	4*	4*	3*	7*	5*
30 mg	27	5*	1*	3*	2*	4*
40 mg	18	3*	2*	0*	0*	9*
Bulinga						
Under 20 years						
20 mg	17	5*	6*	2*	6*	10*
30 mg	22	7*	8*	11*	10*	26
40 mg	19	6*	3*	5*	4*	15
20 years or over						
20 mg	21	7*	4*	2*	7*	16
30 mg	21	2*	0*	2*	2*	14
40 mg	21	2*	0*	3*	0*	7*
Bulamata						
Under 20 years						
30 mg	24	7*	5*	3*	17	26
40 mg	18	4*	5*	3*	18	30
20 years or over						
30 mg	10	0*	2*	3*	6	13
40 mg	9	0*	1*	2*	6	15

*Significant ($P<0{\cdot}05$) reduction compared to pretreatment value.

impact on intestinal morbidity, and particularly bloody diarrhoea, was considerable and lasting.

Discussion

This study should not be considered as a comparison of the long term effects, if they should exist, of praziquantel and oxamniquine; to do that, a randomized study in one single community would be necessary. Reinfection depends primarily on local transmission patterns and immunity factors. One may assume that the potential for protective immunity is similar in the 3 study populations. The intensity and

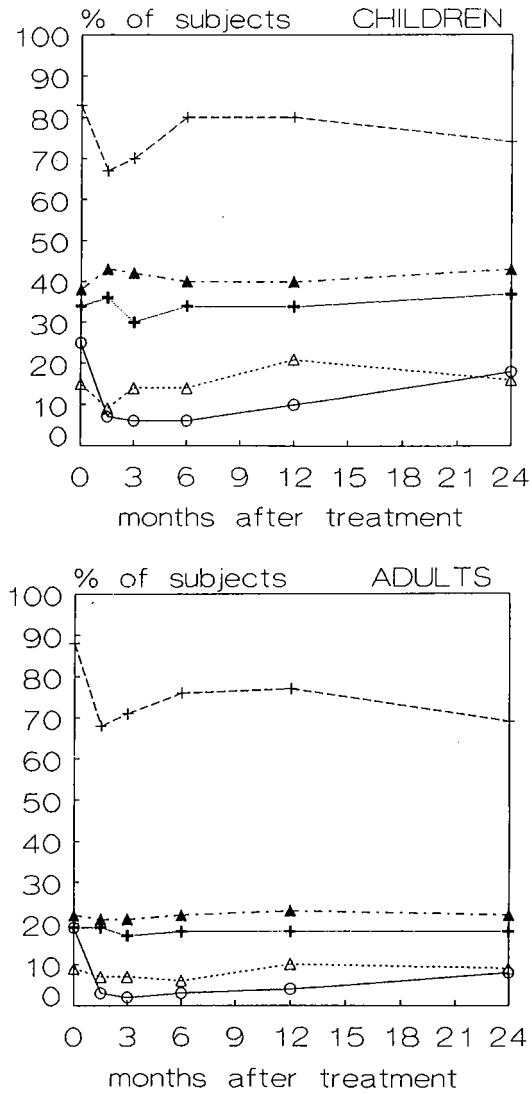

Fig. 4. Development of morbidity in the total study population. Abdominal pain ---+---; hepatomegaly —+—; splenomegaly -·-▲-·-; diarrhoea ---△---; bloody diarrhoea —○—.

dynamics of transmission, however, may vary considerably at short distances (GRYSEELS, 1984, 1988). Thus, the results from each village must be considered separately; comparisons and generalizations must be made with care.

There is no standardized way of representing reinfection data (yet?). It is commonly agreed that, besides the development of the parasitological negativity rate, quantitative measures such as the frequency of heavy infections and mean egg loads are essential, as morbidity is believed to be related to egg output. Many problems arise here. (i) The generally accepted quantitative relationship of egg load to morbidity (WHO, 1985) is not always clear, as discussed elsewhere (GRYSEELS & POLDERMAN, 1987a, 1987b, 1988; GRYSEELS, 1988); its validity after chemotherapy has not been investigated at all. (ii) Egg load classifications may be difficult to standardize: We defined egg loads of over 100 epg as moderate/heavy infections, but in other, even nearby, areas such low egg counts are rather exceptional (POLDERMAN *et al.*, 1985). (iii) Geometric or logarithmic means of egg loads are preferred to arithmetic means because of the (grossly approximate) log-normal distribution of egg counts, but they can be calculated in various ways. To allow for negatives to be included, transformations such as (egg load per gram +1) or (egg count per slide +1) are used. These methods, and particularly the latter, produce considerable distortions if many subjects are negative, which is generally the case after chemotherapy. After comparing different methods, We chose to use untransformed data, from positive egg counts only, for the calculation of geometric means.

Another methodological problem is the lack of a control population. It is clear, however, that ethically as well as operationally it is not feasible to follow-up an untreated population over such a long time.

Finally, it must be stressed that the reinfection rates in this study were based on examinations of a single stool and of varying numbers of patients. Although cohort analysis of the group of fully compliant subjects only confirmed the results shown here, they therefore emphasize only clearly identifiable trends.

In all 3 communities, reinfection was much commoner in children than in adults. In Bulinga and Maramvya, few cured adults contracted new infections in the 2 years after treatment, and almost none had a heavy one. In Bulamata, reinfection in adults was more considerable, but still much less than in children; heavy infections hardly reappeared, and the mean egg loads of those reinfected remained low. In children, the initial negativity rates (GRYSEELS *et al.*, 1987) were lower and reinfection rates much higher, and the long-term parasitological effects were therefore not very satisfying. In Bulamata, almost all children were reinfected in one to 2 years; the frequency of heavy infections, as well as the mean egg loads, rose almost to pretreatment values. In Maramvya, 60 to 80% (depending on the dose given) of the treated children excreted eggs one year after treatment, about half of them over 100 epg; mean egg loads of positive individuals had almost reached pretreatment values. The best results in children were obtained in Bulinga, where transmission was apparently less intense than in the other 2 villages.

The age-dependency of reinfection rates has also been described by others in different areas and circumstances (KATZ *et al.*, 1978; SLEIGH *et al.*, 1981; POLDERMAN *et al.*, 1984; BUTTERWORTH *et al.*, 1984, 1985; WILKINS *et al.*, 1984, 1987). The relative importance of transmission factors compared to host-related factors (particularly immunity) in the transmission dynamics of schistosomiasis has for long been a subject of discussion (WARREN, 1973; BRADLEY, 1972). Recently, BUTTERWORTH & HAGAN (1987) and BUTTERWORTH *et al.* (1987) have reviewed human immunity and concluded that it is an essential, age-related factor in the population dynamics of schistosomes and human reinfection in endemic areas. Although the evolution of infection rates in immigrants indicates that acquired immunity has little or no epidemiological impact in the Rusizi plain population

(GRYSEELS, 1984), it may indeed seem unlikely that the very low reinfection rates in adults can be explained by patterns of water contact only. More comprehensive studies of the transmission dynamics of *S. mansoni* (including water-contact observations) before and after mass chemotherapy, needed to elucidate this point, are now being completed.

Whatever the results, it is clear that in repeated mass treatment programmes, retreatment schedules should be age-specific. It could, for example, be envisaged that yearly treatment should be given to children, while submitting adults to a bi- or tri-annual schedule.

Retreatment schedules may also have to be adapted to local conditions; in this study, reinfection was much less intense in Bulinga than in the 2 other villages. More experience is needed, however, to set up 'rules' linking, for example, initial prevalences or infection intensities to the necessary frequency of retreatment. Such rules can probably not easily be defined: reinfection was more intense in Bulamata than in Maramvya, whereas initial endemicity was certainly higher in the latter. Furthermore, our data also show that transmission intensity may vary locally from one year to another: in Maramvya and Bulinga, little or no further reinfection took place in the second year of follow-up, whereas it continued in Bulamata.

It must further be stressed that, in this study, chemotherapy was—expressly—not complemented by measures for transmission control such as (focal) molluscicide, sanitation or health education. Comparative studies of their complementary impact are now under way. It is, furthermore, not probable that the isolated, incomplete and selective treatment of these populations have had much impact on transmission.

Another observation common to the 3 communities is that the dose-dependency of parasitological negativity and reduction rates tends to fade 6 to 12 months after treatment. Reinfection is a much more important long-term factor than the initial therapeutic efficacy of the drug. From this it may be concluded that, on a community level, suboptimal but cheaper drug dosages may be applied without decreasing the long-term efficacy of the intervention. In any case, the time-consuming procedures needed to dispense the correct doses by weight could be replaced by simpler schedules, as already proposed by POLDERMAN *et al.* (1988).

The predisposition to heavy infection before and after treatment, suggested by KATZ *et al.* (1978) and demonstrated by BENSTED-SMITH *et al.* (1987), was not present in our group. This may be another indication that immunity does not play an overwhelming role in this study population.

The impact of population-oriented chemotherapy on morbidity of schistosomiasis mansoni has been the subject of only a few studies, although 'morbidity control' is the primary aim of the strategy. Recently KLOETZEL & SCHUSTER (1987) evaluated the Brazilian control programme in terms of morbidity in a few selected areas. The parasitological long-term effects of repeated mass treatment were disappointing, but splenomegaly and surgical interventions for portal hypertension had indeed declined. These authors considered, however, that a substantial part of the result was the effect of sanitation.

In another recent study, SUKWA *et al.* (1987) demonstrated a dramatic reduction of infection and morbidity after repeated selective chemotherapy in a Zambian community. However, undertaking 5 surveys and treatment campaigns in 16 months as they did, would not seem to be a likely strategy in any operational programme.

It has been shown (GRYSEELS, 1988) that, in the Rusizi plain, serious hepatosplenic disease is not common, but that intestinal complaints and in particular bloody diarrhoea are clearly associated with the presence, though much less with the intensity, of infection with *S. mansoni*. The pretreatment data confirm that the morbidity is indeed little related to the intensity of infection in this area. They also show that, by comparing villages with different levels of endemicity, differences in morbidity may be more clearly seen than by comparing groups of egg-excreters within one village, as has been demonstrated before (GRYSEELS & POLDERMAN, 1987a, 1987b). Spleen and liver rates are, of course, also affected by varying malaria endemicity (COOSEMANS *et al.*, 1984); schistosomiasis is thought to play a major role at least in adolescents and adults, however (GRYSEELS, 1988), and the 3 study villages here concerned were separated by a few kilometers only.

The post-treatment results show that, even with optimal treatment, there was only a limited impact on hepato- or splenomegaly. Intestinal morbidity, on the other hand, was considerably reduced. The frequency of abdominal pain diminished strongly and durably in Maramvya, and less so in Bulinga and Bulamata. The impact on bloody diarrhoea was very impressive, in all villages, age and treatment groups; this effect lasted for up to 2 years, except for the children in Bulamata, who were quickly and heavily reinfected. The absence of dose-dependency leads again to the conclusion that the impact of lower doses is, in the long term, as good as that of higher ones.

The intestinal morbidity of mansoni schistosomiasis receives little attention in most morbidity studies and control programmes; hepatosplenic disease is generally considered the first priority (WHO, 1985). Nevertheless, high frequencies of intestinal pathology, and dysenteric syndromes in particular, have clearly been linked to schistosomiasis in different foci in Central Africa, where decompensated portal hypertension may be infrequent even if hepatomegaly and splenomegaly are common and attributable to schistosomiasis (GRYSEELS & POLDERMAN, 1987a, 1987b; GRYSEELS, 1988). The present study has shown that the main impact of population chemotherapy in such conditions may be on intestinal morbidity.

On the whole, it is clear that a single selective mass treatment has only a temporary effect on schistosomiasis infection and (hepatosplenic) morbidity. 'Blanket' mass chemotherapy may be more effective then selective treatment, but its feasibility depends on many epidemiological, sociological and economic factors. In any case, *repeated* population therapy, selective or not, combined with sanitation and perhaps molluscicide, needs to be evaluated as the probable eventual strategy for morbidity control, in terms of efficacy (expressed in infection as well as morbidity rates) as well as feasibility. Such studies are now under way in Burundi.

More generally, our results may be a further stimulus to researchers and policy makers to study and define more clearly the concept of 'morbidity control', as well as objective indices to measure its

results.

Acknowledgements

My sincere thanks go to the following persons, whose support and advice have been essential: Dr Mpitabakana, Dr Nyunguka and Mr Simbandumbwe (Burundese Ministry of Health); Dr Storme, Dr Coosemans, Dr Burke, Dr Kivits (Belgian Cooperation Agency); Dr Mott (WHO); Prof Dr Gigase and Prof Dr Eyckmans (Institute for Tropical Medicine, Antwerp); and Dr Polderman (Institute for Parasitology, Leiden), who also critically reviewed the manuscript.

This work would not have been possible without the excellent technical assistance and dedication of our team mates Messrs Nsekerebandya, Gakeme, Banyuruzyeko, Ndarwarukanye, Kanurwe, Ndayshimiye, and the cooperation of the authorities and populations of Maramvya, Bulinga and Bulamata.

The Burundi Schistosomiasis Study and Control Project is a joint programme of the Burundese Ministry of Health and the Belgian Cooperation Agency. This study was co-financed by the Special Programme for Training and Research in Tropical Diseases of the WHO/UNDP/World Bank.

References

Bensted-Smith, R., Anderson, R. M., Butterworth, A. E., Dalton, P. R., Kariuki, H. C., Koech, D., Mugambi, M., Ouma, J. H., Arap Siongok, T. K. & Sturrock, R. F. (1987). Evidence for predisposition of individual patients to reinfection with *Schistosoma mansoni* after treatment. *Transactions of the Royal Society of Tropical Medicine and Hygiene*, **81**, 651–654.

Bradley, D. J. (1972). Regulation of parasite populations. A general theory of the epidemiology and control of parasitic infections. *Transactions of the Royal Society of Tropical Medicine and Hygiene*, **66**, 697–708.

Butterworth, A. E. & Hagan, P. (1987). Immunity in human schistosomiasis. *Parasitology Today*, **3**, 11–16.

Butterworth, A. E., Dalton, P. R., Dunne, D. W., Mugambi, M., Ouma, J. H., Richardson, B. A., Arap Siongok, T. K. & Sturrock, R. F. (1984). Immunity after treatment of human schistosomiasis mansoni. I. Study design, pretreatment observations and the results of treatment. *Transactions of the Royal Society of Tropical Medicine and Hygiene*, **78**, 108–123.

Butterworth, A. E., Capron, M., Cordingley, J. S., Dalton, P. R., Dunne, D. W., Kariuki, H. C., Koech, D., Mugambi, M., Ouma, J. H., Prentice, M. A., Richardson, B. A., Arap Siongok, T. K., Sturrock, R. F. & Taylor, D. W. (1985). Immunity after treatment of human schistosomiasis mansoni. II. Identification of resistant individuals, and analysis of their immune responses. *Transactions of the Royal Society of Tropical Medicine and Hygiene*, **79**, 393–408.

Butterworth, A. E., Wilkins, H. A., Capron, A. & Sher, A. (1987). The control of schistosomiasis—is a vaccine necessary? *Parasitology Today*, **3**, 1–2.

Coosemans, M. H., Wéry, M., Storme, B., Hendrix, L. & Mfisi, B. (1984). Epidémiologie du paludisme dans la plaine de la Rusizi, Burundi. *Annales de la Société Belge de Médecine Tropicale*, **64**, 135–158.

Gryseels, B. (1984). La schistosomiase intestinale dans la plaine de la Rusizi, Burundi: prospection préliminaire. *Annales de la Société Belge de Médecine Tropicale*, **64**, 249–166.

Gryseels, B. (1985). La distribution de *Biomphalaria* et la transmission de *Schistosoma* dans la plaine de la Rusizi, Burundi: étude préliminaire. *Annales de la Société Belge de Médecine Tropicale*, **65**, 49–58.

Gryseels, B. (1988). The morbidity of schistosomiasis mansoni in the Rusizi plain (Burundi). *Transactions of the Royal Society of Tropical Medicine and Hygiene*, **82**, 582–588.

Gryseels, B. & Nkulikyinka, L. (1988). The distribution of *Schistosoma mansoni* in the Rusizi plain (Burundi). *Annals of Tropical Medicine and Parasitology*, in press.

Gryseels, B. & Polderman, A. M. (1987a). The morbidity of schistosomiasis mansoni in Maniema (Zaire). *Transactions of the Royal Society of Tropical Medicine and Hygiene*, **81**, 202–209.

Gryseels, B. & Polderman, A. M. (1987b). *Schistosoma mansoni* morbidity in three Central African foci: intra vs inter-population analysis. *Proceedings of the Interdisciplinary Conference on Primary Health Care in the Tropics, Tropical Diseases and Zoonoses, Geneva*, p. 71.

Gryseels, B. & Polderman, A. M. (1988). Schistosomiasis control: morbidity measurement/morbidity control. In: *Abstracts, XII International Congress for Tropical Medicine and Malaria*, Kager, P. A. & Polderman, A. M. (editors). Excerpta Medica International Congress Series, no. 810.

Gryseels, B., Nkulikyinka, L. & Coosemans, M. H. (1987). Field trials of praziquantel and oxamniquine for the treatment of schistosomiasis mansoni in Burundi. *Transactions of the Royal Society of Tropical Medicine and Hygiene*, **81**, 641–644.

Hackett, W. (1944). Spleen measurement in malaria. *Journal of the National Malaria Society*, **3**, 121–123.

Katz, N., Zicker, F., Rocha, S., & Oliviera, V. B. (1978). Re-infection of patients in schistosomiasis mansoni endemic areas after specific treatment. *Revista do Instituto de Medicina Tropical de São Paulo*, **20**, 273–278.

Kloetzel, K. & Schuster, N. H. (1987). Repeated mass treatment of schistosomiasis mansoni: experience in hyperendemic areas of Brazil. 1. Parasitological effects and morbidity. *Transactions of the Royal Society of Tropical Medicine and Hygiene*, **81**, 365–370.

Polderman, A. M. (1984). Cost-effectiveness of different ways of controlling intestinal schistosomiasis: a case study. *Social Sciences and Medicine*, **19**, 1073–1080.

Polderman, A. M., Kayiteshonga Mpamila, Manshande, J. P. & Bouw huis-Hoogerwerf, M. L. (1985). Methodology and interpretation of a parasitological surveillance of intestinal schistosomiasis in Maniema, Kivu province, Zaire. *Annales de la Société Belge de Médecine Tropicale*, **65**, 243–249.

Polderman, A. M., Gryseels, B. & De Caluwé, P. (1988). Cure rates and egg reduction in treatment of intestinal schistosomiasis with oxamniquine and praziquantel in Maniema, Zaire. *Transactions of the Royal Society of Tropic l Medicine and Hygiene*, **82**, 115–116.

Sleigh, A. C., Mott, K. E., França Silva, J. T., Muniz, T. M., Mota, E. A., Barreto, M. L., Hoff, R., Maguire, J. H., Lehman, J. S. & Sherlock, I. (1981). A three year follow-up of chemotherapy with oxamniquine in a Brazilian community with endemic schistosomiasis mansoni. *Transactions of the Royal Society of Tropical Medicine and Hygiene*, **75**, 234–238.

Sukwa, T. Y., Bulsara, M. K. & Wurapa, F. K. (1987). Reduction in prevalence, intensity of infection and morbidity due to *Schistosoma mansoni* infection in a community following treatment with praziquantel. *Journal of Tropical Medicine and Hygiene*, **90**, 205–211.

Warren, K. S. (1973). Regulation of the prevalence and intensity of schistosomiasis in man: immunology or ecology? *Journal of Infectious Diseases*, **127**, 595–609.

WHO (1985). *The control of schistosomiasis—Report of a WHO expert committee*. Geneva: World Health Organization, *Technical Report Series*, No. 728.

Wilkins, H. A., Goll, P. H., Marshall, T. F. de C. & Moore, P. J. (1984). Dynamics of *Schistosoma haematobium* infection in a Gambian community. II. Acquisition and loss of infection. *Transactions of the Royal Society of Tropical Medicine and Hygiene*, **78**, 227–232.

Wilkins, H. A., Blumenthal, U. J., Hagan, P., Hayes, R. J. & Tulloch, S. (1987). Resistance to reinfection after treatment of urinary schistosomiasis. *Transactions of the Royal Society of Tropical Medicine and Hygiene*, **81**, 29–35.

Received 25 January 1988; revised 24 May 1988; accepted for publication 30 June 1988