

IMPACT OF REPEATED COMMUNITY-BASED SELECTIVE CHEMOTHERAPY ON MORBIDITY DUE TO SCHISTOSOMIASIS MANSONI

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Abstract. The impact of repeated chemotherapy on morbidity due to schistosomiasis mansoni was evaluated in Gihungwe (initial prevalence 58%) and Buhandagaza/Kizina (33%), two village clusters in Burundi. Surveys were carried out with reference to the first treatment (month 0) at months -6, -3, 0, 3, 6, 9, 12, 24, and 36. Praziquantel (40 mg/kg) was given at months 0, 12, 24, and 36 to those showing eggs in the feces with a single 28-mg Kato slide. At each survey, duplicate Kato smears were examined, and all participants responded to a standardized medical history interview and underwent a clinical examination. In the three preintervention surveys, spleen and liver rates remained stable at the community and the individual level. The frequencies of diarrhea and abdominal pain varied to some extent, but they were consistently higher in the most heavily infected villages and age groups and remained relatively stable at the individual level. At the final survey, the prevalence of infection had decreased to 25%, and the frequency of diarrhea from 19–26% to 10% in both village clusters. This impact was strongest in the younger age groups. The frequency of abdominal pain was reduced only at the short term and in selected age groups. Organomegaly decreased only to a limited extent in those treated, and increased in those not treated, possibly due to the impact of malaria. The net result was that no measurable impact of the treatments on organomegaly at the community level could be demonstrated. In the light of these results, the relevance of community-based chemotherapy in moderate foci is questioned.

Community-based chemotherapy is widely applied for the control of schistosomiasis mansoni. However, evaluations of the strategy in terms of its main objective, reduction of morbidity, are still scarce.¹ In Burundi, there has been an attempt to justify and develop a national schistosomiasis control program by assessing infection levels as well as morbidity, and the extent to which they are reduced by chemotherapy.^{2,3} The study reported here was carried out to evaluate the impact of repeated selective treatment with praziquantel on schistosomiasis morbidity at the community level. The impact on prevalences and intensities of infection has been reported in detail elsewhere.⁴

MATERIALS AND METHODS

The study took place in four neighboring villages in the Rusizi Plain, the western lowland of Burundi, which were regrouped in two clusters, Gihungwe T1/T2 (combined population 748, combined initial prevalence 58%), and Buhandagaza/Kizina (population 857, prevalence 33%). The Rusizi Plain is a valley (altitude 700–

1,000 m) enclosed by mountains. It covers an area of 1,000 km² and has a tropical climate. The population is approximately 140,000 inhabitants, mainly cotton and rice farmers and their families. The people are dispersed mostly along roads or in small villages. Gihungwe T1/T2 consists of two roads with mostly cotton farmers; Buhandagaza and Kizina are more compact villages, with mostly rice and subsistence farmers. More details on the area and the study villages are provided elsewhere.^{4,5} All inhabitants were invited to participate in the study. The first seven surveys took place at intervals of three months three times before and four times after the first treatment. Two more surveys and treatments were performed thereafter at yearly intervals. Thus, with reference to the first treatment (month 0), surveys took place at months -6, -3, 0, 3, 6, 9, 12, 24, and 36. At each survey, all participants submitted to a stool examination based on duplicate 28-mg Kato slides of one fecal sample. One slide was examined 30–180 min later at the site, the other 24–72 hr later in the field station.⁴ After the surveys at months 0, 12,

TABLE 1
Number of individuals at consecutive surveys

Age (years)	Survey number								
	1	2	3*	4	5	6	7*	8*	9*
Gihungwe									
0-9	219	205	217	213	210	202	206	205	207
10-19	152	137	138	135	138	141	133	124	109
20-39	216	194	195	188	187	189	188	174	175
≥40	161	152	156	159	158	154	152	146	143
All	748	688	706	695	693	686	679	649	634
Buhandagaza/Kizina									
0-9	282	247	255	216	257	249	242	226	191
10-19	153	130	123	117	133	131	124	113	108
20-39	251	214	205	173	209	221	202	190	171
≥40	171	152	149	138	152	151	146	136	124
All	857	743	732	644	751	752	714	665	594

* Surveys with selective treatment.

24, and 36, a single dose of praziquantel (40 mg/kg) was given to individuals with *Schistosoma mansoni* eggs in the slide examined at the site, simulating the screen-and-treat approach of the control program in Burundi. The parasitologic data presented are those obtained in the combined Kato slides.

At each survey, all individuals responded to a standardized medical history interview in the local language and underwent a clinical examination. The history focused on general and specific problems or symptoms (diarrhea, bloody diarrhea, abdominal pain) that had occurred during the three previous months. Symptoms were considered significant if at least two episodes of one or more days had occurred during that time. The number of and reason for visits to health centers and the number of days the individuals were unable to attend work or school in the past three months were recorded. The clinical examination consisted of the measurement in a supine position of liver enlargement (right anterior axillary line, midsternal line) in cm under the costal arch and spleen enlargement according to Hackett⁶ and Gryseels.⁷ All histories and examinations were done by the same experienced medical officer (LK), who was familiar with the population but unaware of the parasitologic status of the subjects. Egg counts are expressed in eggs per gram feces (epg). Individuals were assigned to age groups on the basis of their age in the initial survey. Differences between proportions were tested for significance by the chi-square test.

RESULTS

The number of individuals examined and treated in the different surveys is given per village cluster and per age group in Table 1. The age-specific prevalences of infection are summarized in Table 2 and have been described in more detail elsewhere.⁴ The overall morbidity parameters are summarized in Figures 1 and 2; age-specific data are further detailed in Table 3.

Three months after the first treatment, the parasitologic cure rate in those treated was 73% in Gihungwe and 83% in Buhandagaza/Kizina. The prevalences at the community level were reduced only by 50% and 46%, respectively (Table 2). Many people who were negative on the single-slide screening and therefore not treated were, in fact, positive on the duplicate slide or one or more of the slides in the preintervention surveys.⁴ Reinfection after the first treatment was most intense in Gihungwe and in younger age groups. One year after the second treatment, prevalences and intensities had further decreased in Gihungwe only; one year after the third treatment, there was no further decrease in either village group. The final prevalence, one year after the third treatment, was approximately 25% in both village groups, with the prevalence of infections greater than 100 epg approximately 5%.

In the three surveys before the first treatment, the frequency of bloody diarrhea varied to some extent in both village groups. However, it was consistently 2-3 times higher in Gihungwe than in Buhandagaza/Kizina in all age groups, and

TABLE 2
Percent prevalences of infection*

Age (years)	Village	Survey number								
		1	2	3†	4	5	6	7†	8†	9†
All	G	60	57	66	33	46	47	50	26	26
	B	33	36	42	23	27	28	29	23	25
0-9	G	41	43	59	33	51	53	54	32	32
	B	22	22	27	20	21	21	26	31	28
10-19	G	84	82	89	48	62	66	70	38	41
	B	48	56	64	35	43	42	39	34	32
20-39	G	60	58	62	31	40	38	38	24	23
	B	34	37	45	20	23	29	28	16	20
≥40	G	62	54	62	31	32	32	41	21	10
	B	33	38	47	22	27	26	25	11	23

* G = Gihungwe; B = Buhandagaza/Kizina.
† Surveys with selective treatments.

higher in children and adolescents than in adults in both villages. The frequency of abdominal pain was consistently more than 60% in both village clusters and in most age groups.

Liver and spleen enlargement rates were relatively stable over the six months preintervention survey period. The overall frequency of hepatomegaly was slightly higher in Gihungwe

than in Buhandagaza/Kizina. However, in the 10-19- and ≥ 40-year-old age groups, it was consistently and significantly higher in Gihungwe in all pretreatment surveys. Splenomegaly was more frequent in Buhandagaza/Kizina, with the largest difference in the age group 0-9 years of age.

In the three different pretreatment surveys, the

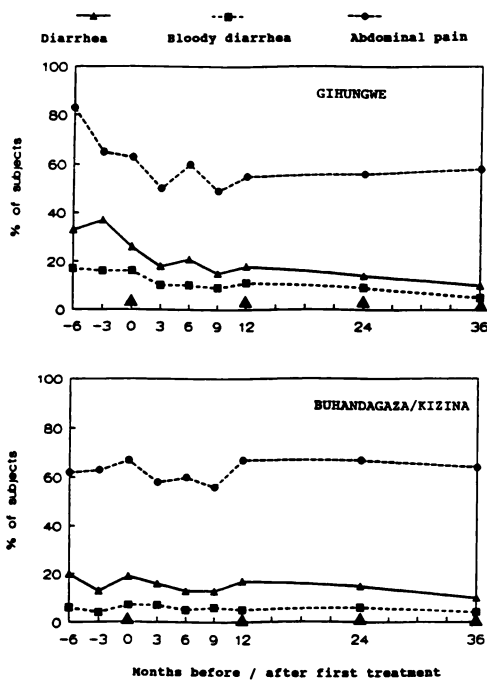


FIGURE 1. Frequencies at consecutive surveys of diarrhea, bloody diarrhea, and abdominal pain in the two village clusters (all ages). Arrowheads indicate when treatment with praziquantel was given.

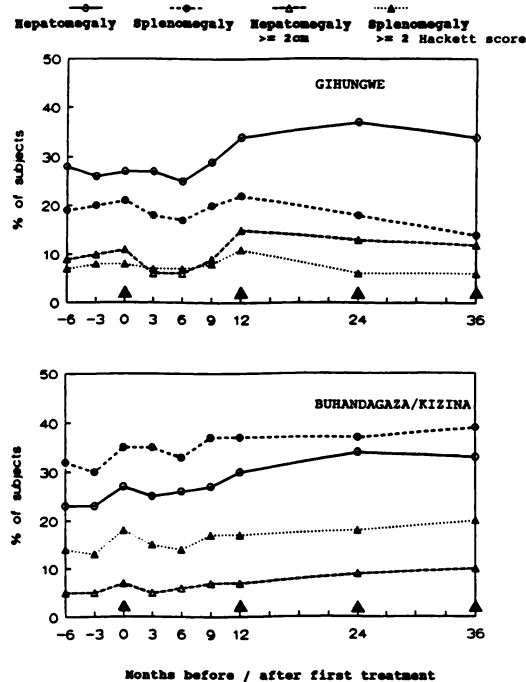


FIGURE 2. Frequencies at consecutive surveys of hepatomegaly and splenomegaly in the two village clusters (all ages). Arrowheads indicate when treatment with praziquantel was given.

TABLE 3
Age-related morbidity*

Age (years)	Village	Survey number								
		1	2	3†	4	5	6	7†	8†	9†
Frequency of diarrhea										
0-9	G	44	53	38	32	32	26	33	21	18
	B	28	22	24	25	18	23	30	25	16
10-19	G	34	37	31	13	25	15	15	10	6
	B	20	15	28	23	20	14	20	18	12
20-39	G	30	26	19	10	14	9	7	14	7
	B	13	8	14	10	9	8	9	10	5
≥40	G	23	32	15	11	12	8	11	6	6
	B	18	5	11	6	6	5	4	4	6
Frequency of hepatomegaly										
0-9	G	43	44	48	50	48	51	61	68	63
	B	36	38	48	46	47	51	54	62	49
10-19	G	35	34	36	36	28	31	38	39	31
	B	21	23	26	24	29	27	33	33	44
20-39	G	10	7	6	5	7	9	11	12	13
	B	7	6	6	6	8	8	10	11	22
≥40	G	22	18	16	15	15	15	20	23	21
	B	14	12	13	12	14	12	16	18	15
Frequency of splenomegaly										
0-9	G	25	27	28	23	22	24	30	24	20
	B	46	42	49	51	50	60	58	57	48
10-19	G	22	31	28	24	22	21	26	26	14
	B	33	34	36	35	33	39	42	47	50
20-39	G	12	10	13	11	11	14	17	10	11
	B	17	16	22	22	22	20	22	21	33
≥40	G	12	13	14	13	12	14	14	12	8
	B	18	18	22	22	18	20	18	19	23

* Values are percentages. G = Gihungwe; B = Buhandagaza/Kizina.
† Surveys with selective treatment.

occurrence of symptoms was relatively stable at the individual level, i.e., they were usually found in the same subjects. Of those complaining of diarrhea at survey 3 in Gihungwe, 63% and 51% had already reported diarrhea at surveys 1 and 2, respectively; of those who did not report diarrhea at survey 3, 30% and 28% had reported diarrhea at surveys 1 and 2, respectively. In Buhandagaza/Kizina, these figures were 31% and 33% versus 9% and 19%, respectively. Of those with hepatomegaly at survey 3 in Gihungwe, 84% had also shown hepatomegaly at survey 1 and 80% at survey 2. Of those without hepatomegaly at survey 3, only 7% and 8% had shown hepatomegaly at surveys 1 and 2, respectively. In Buhandagaza/Kizina, these figures were 81% and 75% versus 3% and 5%. For splenomegaly, the figures were 55% and 66% versus 7% and 8% in Gihungwe, and 78% and 71% versus 6% and 12% in Buhandagaza/Kizina.

The relationship between egg counts and mor-

bidity rates in the various pretreatment surveys was generally consistent with those observed in earlier, cross-sectional morbidity studies in the area.⁷⁻⁹

At surveys 4-7 in the year after the first treatment, the frequency of diarrhea was reduced considerably in all age groups in Gihungwe (Figure 1 and Table 3). At surveys 8 and 9, one year after the second and third treatments, respectively, the frequency of diarrhea was further reduced in the groups 0-9 and 10-19 years of age, but not in the older age groups. At the final survey (9) after three yearly treatments, the overall frequency of reported diarrhea was 10%, a reduction from 26% at survey 3, just before the first treatment. Evidence for a reduction in abdominal pain was seen only at survey 4, three months after the first treatment. The causal relationship seemed doubtful because there were considerable variations in the frequency of abdominal pain in the preintervention surveys (1-

TABLE 4
Morbidity rates in relation to treatment status*

Village	Status	Survey number						
		3†	4	5	6	7†	8†	9†
Frequency of diarrhoea								
Gihungwe	T	33	17	24	15	20	13	13
	N	17	18	19	14	15	14	10
Buhandagaza/Kizina	T	22	13	11	13	15	15	11
	N	18	18	14	14	18	15	10
Frequency of hepatomegaly								
Gihungwe	T	33	32	28	31	36	45	45
	N	18	22	22	23	31	32	33
Buhandagaza/Kizina	T	29	29	27	25	28	40	43
	N	24	22	26	27	31	32	32
Frequency of splenomegaly								
Gihungwe	T	26	20	19	21	24	22	26
	N	14	14	15	15	20	15	12
Buhandagaza/Kizina	T	40	33	29	37	36	44	35
	N	31	34	34	37	37	36	40

* Values are percentages. T = treated at the previous treatment survey; N = not treated at the previous treatment survey.

† Surveys with selective treatment.

3) and in subsequent surveys (5–7). There were no substantial alterations in this factor at surveys 8 and 9 after the second treatment.

In Buhandagaza/Kizina, the frequency of diarrhoea was reduced at surveys 4–6, 6–9 months after the first treatment compared with survey 3, just before the first treatment. It was further reduced at surveys 8 and 9, one year after the second and third treatments, respectively. At the final survey (9) one year after the third treatment, the overall frequency of reported diarrhoea was 10% compared with 19% at survey 3. The reduction was greatest in the group 10–19 years of age. It should be noted that, particularly in this age group, the frequency of diarrhoea varied substantially in surveys 1–3 before any treatment had been given. The frequency of abdominal pain was reduced in the surveys 3–9 months after the first treatment compared with survey 3. However, in this village cluster the frequency of abdominal pain varied strongly in the pretreatment surveys (1–3), particularly in the younger age groups. At surveys 8 and 9 one year after the second and third treatments, respectively, the frequency of abdominal pain was not notably different from pretreatment levels.

The overall frequency of hepatomegaly in Gihungwe was not affected by the first treatment (Figure 2). Age-related analysis showed no significant or consistent trend (Table 3). The frequency of gross hepatomegaly showed a tem-

porary decrease that was significant in all age groups up to 40 years of age. The overall frequency of splenomegaly tended towards a temporary decrease (Figure 2). Age-specific analysis shows this trend in the age groups up to 20 years old (Table 3). Splenomegaly grading Hackett score = 2 or more showed no significant evolution overall or in any age group. After the second and the third treatments, spleen rates were further reduced, but hepatomegaly rates only showed a decrease in the group 10–19 years of age after the third treatment and in increase in other age groups. In Buhandagaza/Kizina, the overall liver and spleen rates were not markedly affected by any of the treatments and actually showed an increase over the study period, particularly in the group 10–19 years of age.

Table 4 presents the results of those who had received praziquantel during the treatment cycle prior to a given survey and those who did not. It shows that in both village groups, the reduction of diarrhoea after the first treatment was observed mainly in those who had received praziquantel, although smaller fluctuations were also observed in those not treated. At surveys 8 and 9 one year after the second and third treatments, respectively, the pattern became irregular in relation to (re)treatment status; at the final survey (9), diarrhoea was reduced in those treated as well as in those not treated at survey 8, one

year earlier. However, many of those not treated at survey 8 had received treatment at surveys 3 and/or 7.⁴ Table 4 also shows that in both village groups, the frequency of hepatomegaly did not decrease after the first treatment in those who received praziquantel, but actually increased in those who had not been treated; this trend was present in all age groups up to age 40. The second and third treatments did not result in a further reduction in hepatomegaly either in the treated or untreated groups. For splenomegaly, the first treatment was followed by a temporary reduction in those who had received praziquantel. This trend was present in all age groups up to age 40. In those who had not received praziquantel, the frequency of splenomegaly increased. After subsequent treatments, no consistent further reduction of spleen rates was observed.

The number of visits to health posts and the number of days of incapacity could not be recalled accurately or even approximately by many of the responders and are not shown. In general, these data were reported in a hesitant and unreliable manner. In any case, they could not be related to schistosomiasis in the preintervention surveys and did not decrease after treatment. Fourteen study participants in Gihungwe and 39 in Buhandagaza/Kizina were reported to have died during the study period. These deaths, attributed mainly to fever and old age, could not be adequately documented.

DISCUSSION

Morbidity reduction is the basic objective of chemotherapy-based schistosomiasis control strategies.¹ Thus, the impact of population treatment on morbidity rates is more relevant to health policy than its effect on prevalences and intensities of infection rates, regardless of the interest such data may have epidemiologically.⁴ In this respect, the impact at the community level is of greater interest than on the group of treated individuals as such.

We have tried to validate the morbidity parameters by measuring them repeatedly in the preintervention surveys. Recording diarrhea and abdominal pain through medical histories is easily biased, and we standardized the interviews as much as possible. The consistency of most individual results at the repeated pretreatment surveys indicates that the records are relatively

reliable. However, important variations during the pretreatment period were observed, particularly in Buhandagaza/Kizina, and changes after treatment must be interpreted with caution, especially since we could not control for other causes of intestinal pathologies. Liver and spleen enlargement also remained relatively consistent during the preintervention period, at the community as well as at the individual level.

The preintervention morbidity patterns were in agreement with those observed in several earlier morbidity studies in this and nearby endemic areas.^{2, 7-9} Diarrhea and hepatomegaly were considerably and consistently more frequent in Gihungwe (high prevalence of infection) than in Buhandagaza/Kizina (low prevalence), particularly in people less than 20 years of age. Splenomegaly, however, was more frequent in Buhandagaza/Kizina, particularly in the group 0-9 years of age, confirming the findings of earlier studies that showed that malaria is the main determinant of splenomegaly in this area, although schistosomiasis may play an additional role in older children and adults.^{7, 10}

The decrease of intestinal complaints after treatment was significant and appeared convincing, even with the caution expressed above, particularly in Gihungwe. In Buhandagaza/Kizina, the impact was less striking when compared with preintervention variations, although in the group 10-19 years of age, a relatively important reduction of diarrhea appears to have been achieved. The reduction of the frequencies of diarrhea to the same level in both village groups (Figure 1) is quite remarkable and matches the evolution of infection rates, suggesting that the fraction attributable to schistosomiasis had indeed been strongly reduced. Confounding factors, such as a coincidentally concurrent reduction of other, unrelated intestinal pathology cannot be excluded, however. The reduction of abdominal pain in young children was significant in the short term, but was not maintained.

The impact of the treatments on hepatomegaly and splenomegaly was not convincing. On the community level, there is at most a temporary decrease after the first treatment in the younger age groups; over the whole survey period, if anything, an increase is observed. When treatment-specific group rates are considered, however, in both village groups a marked increase of liver and spleen rates was observed in those who did not receive treatment, whereas this was

not or much less the case in those who were treated. A possible explanation is that malaria morbidity may have increased during the study period due to spreading chloroquine resistance in the area.¹¹ Praziquantel treatment may still have reduced the organomegaly attributable to schistosomiasis. Whatever the explanation, it can only be concluded that the impact of schistosomiasis-specific intervention on hepatomegaly and splenomegaly has not matched the considerable reduction of prevalences and intensities of infection, and that the value of organomegaly rates as an indicator in monitoring schistosomiasis-related morbidity is limited. Ultrasound studies elsewhere have led to the same conclusion.^{12, 13}

As far as we could delineate, there was no indication of severe pathology, such as hematemesis or schistosomiasis-related mortality. Indicators of general well-being, such as the number of days of incapacity or of visits to health posts, could not be related to schistosomiasis or the treatments but clearly require a more focused protocol.

In a few other studies on schistosomiasis *mansoni* in subSaharan Africa, morbidity as well as infection rates have been monitored after community-based treatment. In an earlier study in Burundi, a group of infected and treated individuals, rather than a community, was followed after a single treatment with various doses of oxamniquine or praziquantel. A reduction of diarrhea, but not of organomegaly, was observed.¹⁴ Disappointing results in terms of reduction of organomegaly and intestinal complaints were reported from a control trial in Tanzania (Rugemalila JB, Gabone RM, unpublished data). A marked reduction of hepatomegaly after eight years of targeted chemotherapy was reported in the intense focus of Maniema (Zaire), in spite of persisting high prevalences and intensities of infection.¹⁵ However, the severe organomegaly in that area was almost entirely related to schistosomiasis.¹⁶ In Zambia, considerable reductions of infection rates, bloody diarrhea, and hepatomegaly were observed after five campaigns of selective chemotherapy in a 16-month period.¹⁷ However, such a frequent treatment would seem a difficult approach in an operational control program.

In conclusion, repeated selective chemotherapy for schistosomiasis *mansoni* apparently led to a considerable decrease of intestinal morbidity

in these study populations, but the impact on organomegaly was limited. Considering its high cost and low sustainability, the relevance of repeated community-based chemotherapy in these circumstances is therefore questionable, although it may be a valid short-term strategy in intense foci with severe morbidity.^{18, 19} If, as in our study area, hepatosplenic morbidity is only apparent from mild organomegaly without clear functional consequences, and is furthermore not clearly affected by chemotherapy, then the main objective of the intervention becomes reduction of intestinal morbidity. This objective may better be pursued with a comprehensive and integrated strategy for diarrhea control through primary health care, including adequate curative care for symptomatic cases and safe water supplies.

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