

Final Grant Report

Please submit your report electronically to your Program Coordinator and include "Annual Progress Report – Grant ID" in the subject line using the form that begins on page 4.

The Final Grant Report contents include:

Section A

I. Summary Information

Grant ID#: 36202

Report Due Date: 29th February 2012 **Date Range of Activities Reported:** 10/2006-12/2011

Project Title: The evaluation of integrated control of Neglected Tropical Diseases in Africa

Organization Name: Schistosomiasis Control Initiative
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Grant Amount (U.S. dollars): \$9,975,810 **Project Duration (months):** 63

Project End Date: 31st Dec 2011

Has this project been granted a no-cost extension? Yes

Geographic Location(s) of project UK, Burkina Faso, Niger, Uganda and Tanzania

Report Prepared by: Alan Fenwick **Date Submitted:** 29th Feb 2012

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II. Annual Progress Report – Narrative

Gates II Annual Progress Report – Narrative

A MAJOR ACTIVITIES AND MILESTONES

Since 2006, the SCI has facilitated the implementation of integrated NTD control in Burkina Faso, Niger and Uganda through co-funding, utilizing grants from USAID and the Gates Foundation. All three countries have been able to build on the experience of the different vertical programmes already in existence to successfully implement a national integration strategy, ultimately resulting in the treatment of millions of individuals against NTDs.

However, the USAID NTD Program does not include funds for the important process of monitoring and evaluation of the integrated control programmes; an aspect which forms the heart of the SCI's Gates Foundation grant. It is through the operational research facilitated by this grant that the merits of the integrated strategy can be demonstrated, with the aim of subsequently leveraging further funding for integrated NTD control, encouraging the development of such programmes within endemic countries, and providing guidance on implementation. Extensive data collection has been undertaken within the framework of the grant, providing a wealth of information surrounding the programmes relating to disease burden, social awareness, attitudes to treatment, improvements in health status as a result of treatment, and costs associated with integrating multiple vertical control programmes. The analysis of these data (presented below as well as ongoing analysis) is expected to provide the evidence needed to justify integration of NTD programmes as a priority in public health.

Following the end of the original grant period, a portion of the grant remained unspent. Following discussions with the Gates Foundation, a No Cost Extension (NCE) to the project was arranged, with the aim of answering a series of additional operational research questions, identified as being of particular importance to the successful current and future running of integrated NTD control programmes. The achievements of the SCI against both the original grant objectives and those of the NCE are detailed in the body of the document.

The SCI continues to publish analysis and results from its programmes wherever possible, in order to help inform the design of future NTD control programmes. To date, the SCI has published approximately 130 peer-reviewed articles and 7 book chapters produced (see Appendix 1)

Activity 6 Implementation of 'Health Package'

Implementation of the integrated NTD 'Health Package' has been possible at scale in Niger, Burkina Faso, and Uganda through USAID support. The Tanzania NTD programme was launched in 2009 and has increased in scale annually since then, now that funds have been guaranteed. See Table 5 for treatment numbers.

The implementation of the integrated NTD control in both Niger and Burkina Faso from 2006-2010 was led by the SCI in collaboration with the local Ministries of Health. In addition to providing technical and financial assistance, the SCI also coordinates M&E activities that evaluate the impact of the PCT. In 2011, the USAID sub-grant was re-awarded to Helen Keller International (HKI) who will now assist the integrated NTD control programmes for the next five years. The implementation of the NTD programme in Uganda was managed initially by SCI and subsequently by RTI International, with SCI providing technical assistance and funds for monitoring and evaluation of the integrated programme.

Niger

Since 2006 Niger's MoH started to scale up the integrated control of five NTDs. Prior to Niger's integrated NTD control programme, there were established control programmes for Schistosomiasis, STH, trachoma and onchocerciasis, but there had been no mass treatment for lymphatic filariasis. Four pharmaceutical companies committed to donate their products (ivermectin, albendazole, mebendazole and azithromycin) to the MoH, who were able to arrange the delivery of these drugs, and Niger has brought together domestic and international partners to implement the PCT as needed throughout the country. In 2007 in the first year of integrated control, 19 districts were targeted for integrated treatment, of which nine districts were targeted for LF (and onchocerciasis), 11 districts were targeted for schistosomiasis, 17 were targeted for trachoma and 17 were targeted for STH. A total of 2,223,903 people were treated with both ivermectin and albendazole for LF, 1,395,163 people were treated with praziquantel for schistosomiasis, 5,175,245 people were treated for trachoma. Of all the individuals treated, 3,164,014 received albendazole which also treats for STHs.

By 2010 treatment had progressively extended to cover 38 districts, of which 27 districts were targeted for LF (and onchocerciasis), 32 districts were targeted for schistosomiasis, eight were targeted for trachoma and 32 were targeted for STH. The 2010 PCT reached a total of 7,464,096 people with ivermectin and albendazole against LF, 3,011,576 were treated with praziquantel against schistosomiasis, 3,150,155 people were treated with azithromycin against trachoma and 70,043 children under 6 months of age were given tetracycline against trachoma. Of those individuals treated, a total of 7,772,064 received albendazole against STH.

Burkina Faso

In 2009, Burkina Faso was the first of the USAID supported countries to achieve country-wide integrated treatment against all five NTDs – an ambitious effort for a programme established in 2007. However, prior to the start of integrated NTD control, Burkina Faso had previously established vertical national lymphatic filariasis (LF), STH and schistosomiasis

control programmes. As an ex-Onchocerciasis Control Program (OCP) country, Burkina Faso had also succeeded in virtually eliminating onchocerciasis as a public health problem prior to integration. Building on the existing programmes, the Burkina Faso Ministry of Health scaled-up and integrated the PCT against five NTDs (schistosomiasis, onchocerciasis, LF, trachoma and STH) to national level, with trachoma being the newest national programme to be incorporated into MoH control efforts. In 2007, in the first year of integrated control, three districts were targeted and a total of 1.01 million individuals treated. This was scaled up to 36 districts in 2008 (4.42 million individuals treated) and by 2009 reached 100% geographic coverage in all 55 (now 63) districts (12.4 million individuals treated). In 2010 integrated NTD treatment continued on a nationwide level with over 12.7 million people receiving treatment.

The success of the scale-up to nationwide integrated NTD control can be attributed to several factors, (1) the excellent commitment and financial contribution from the Burkina Faso MoH who brought together local and international partners to implement the PCT, (2) the donation of several essential drugs from pharmaceutical companies, (3) large-scale funding received from donors such as USAID and the Gates Foundation through the SCI, and (4) funding and technical support from the LF Support Centre (LFSC) Liverpool and LFSC Atlanta.

	Burkina Faso				Niger			Uganda		
	2007	2008	2009*	2010	2008	2009	2010	2008	2009*	2010-2011*
Schistosomiasis	756,000	3,451,503	2,923,088	4,702,956	1,338,938	1,515,472	2,716,775	659,520	2,968,006	2,831,296
Lymphatic Filariasis		7,433,840	6,467,770	12,326,907	3,849,412	6,523,176	7,802,679	617,835	3,036,950	11,694,724
Soil-transmitted Helminths		7,433,840	6,467,770	12,326,907	3,945,152	7,303,278	7,802,679	10,295,834	5,503,111	5,857,694
Trachoma	1,032,285	997,185	3,405,260	2,893,060	5,686,468	7,526,076	n/a	4,311,922*	0	7,027,046
Onchocerciasis	150,961	24,562	190,482	n/a	n/a	n/a	n/a	1,659,396	2,443,597	680,000**
Total Treatments	1,010,000	19,340,930	19,454,370	12,692,227	14,819,970	22,868,002	18,322,133 (excl. trachoma)	17,544,507	13,951,664	25,259,464

*Targeted treatment numbers. **Onchocerciasis only districts. Does not include eligible populations in 19 LF/onchocerciasis co-endemic districts

Table 5. Treatment numbers in integrated NTD treatment zones

Uganda

Uganda has now implemented several rounds of integrated NTD treatment. In November/December 2007, 28 districts were treated followed by a further 19 districts in April/May 2008. The third round was carried out in November/December 2008 with 28 districts being re-treated for NTDs and an additional 11 districts being treated for the first time under the NTD programme. Prior to the integrated NTD programme there had been no mass treatment for trachoma infection as part of the SAFE strategy. Scale up has continued since 2008 with the NTD programme reaching 72 eligible endemic districts in 2009 and 2010. Eligible districts for the NTD programme are those that contain 2 or more NTDs at average district threshold prevalences (>1% for LF and onchocerciasis; > 10% for schistosomiasis and STHs). Achievement of national coverage and reporting of the NTD programme has been complicated by on-going administrative changes in Uganda, leading to an increase in the number of districts from the 56 at present at the 2002 census. For example, 58 of the now 84 districts in Uganda had been treated by the end of 2008, but by 2011, there were 112 administrative districts in total in Uganda.

In 2011, preventative chemotherapy was further scaled up to 84 districts, with preliminary data indicating 22, 688,755 treatments having taken place in total for the 5 NTDs in the 77 districts which have reported so far.

Major success of the NTD programme include the initiation of PCT for trachoma, reaching all highly endemic districts, increased geographical scale-up of onchocerciasis and schistosomiasis treatment, increase in the regularity of LF treatment and the first implementation of PCT in some of the many war-torn districts of northern Uganda.

Tanzania

The integrated NTD programme in Tanzania was launched in 2009. This was based primarily on the Community Directed Treatment with Ivermectin (CDTI) approach. In 2009 small scale treatment was implemented primarily in areas that were co-endemic for onchocerciasis and at least one other NTD. In 2009 36 out of the 132 districts were treated. The programme has steadily scaled up year by year with a total of 93 districts targeted to receive integrated treatment in 2012 which represents 50% coverage. Some additional mapping activities especially for trachoma are still required.

***Activities 8 and 10 Measure the reduction of overall prevalence, intensity and transmission of NTDs. Determine the extent to which integrated control programmes produce measurable effects on improved nutritional status, reduced morbidity, and improved school attendance.*¹**

The SCI, in collaboration with senior international epidemiologists and in-country scientists and technicians, developed a Monitoring and Evaluation (M&E) protocol to assess disease burden in relation to integrated NTD treatment. The first protocol was developed for Uganda and subsequently modified for Burkina Faso and Niger. Modifications were based on disease epidemiology, geography, feasibility and treatment history, and country-specific protocols are available on request.

The National Institute for Medical Research in Tanzania is leading the M&E of their NTD programme. The SCI provided technical assistance and participated in the working sessions to develop their independent M&E protocol which draws on the key components of the overall SCI protocol. Longitudinal analysis has been carried out for the Phase I Tanzanian schools where baseline data was collected in 2005 and follow-ups occurred in 2006 and 2008. This analysis showed evidence of programme effectiveness both for prevalence and intensity of *S. haematobium*. Furthermore, 2009 data from a subset of Phase I (3rd follow-up) and Ukerewe communities (2nd follow-up) have now been entered and cleaned. These data are largely cross-sectional but it appears that some longitudinal follow-up was possible at the outset of the programme. Analysing the longitudinal data alone from the Phase I and Ukerewe communities provides some evidence of decreasing *S. mansoni* intensity between baseline and follow-up but this analysis needs expanding to include the much larger cross sectional sample.

¹ No school attendance data have been collected.

Uganda integrated programme

Uganda carried out data collection in seven districts at baseline. In one of these districts (Oyam) prevalence of each of the NTDs was found to be very low or zero and was dropped from the study after baseline. In each of the six other districts, first and second year follow-up data have been collected, entered in-country, cleaned and analysed. The final district to complete data collection was Kitgum, as part of the no-cost extension. Perhaps due to the history of vertical treatment for schistosomiasis and STH, evidence of programme effectiveness for these species was less pronounced than with new deworming initiatives. However, the chemotherapy appeared successful in reducing the intensity of *Schistosoma mansoni* and hookworm:

Parasite	Stage	Intensity as per model of log-transformed egg count	Percentage change in intensity from baseline	p-value for comparison with baseline
<i>Schistosoma mansoni</i>	Baseline	2.60		
	Follow-up 1	2.12	-18.7	p<0.001
	Follow-up 2	2.01	-22.9	p<0.001
Hookworm	Baseline	1.23		
	Follow-up 1	1.19	-3.9	NS
	Follow-up 2	0.84	-31.9	P<0.001

The starting prevalence of *Ascaris* and *Trichuris* was very low but the programme still appeared to reduce *Ascaris* prevalence significantly. Although the prevalence of *Trichuris* did decrease, changes were not statistically significant.

This integrated dataset is very rich and contains parasitological records of schistosomiasis, STH, trachoma, onchocerciasis, lymphatic filariasis and malaria over the course of the program. It also contains morbidity data including anaemia, nutritional status and ultrasonography. Substantial further analysis is planned to include:

- Complete evaluation of programme effectiveness across all measured diseases and morbidities
- Cluster analysis to explore co-infection and co-morbidity and the impact of the integrated programme thereon
- Impact of single versus mixed infections on morbidity
- An investigation of potential bias resulting from loss to follow-up

The dataset has the potential to yield several publications in the future.

Niger vertical programme

From November 2009 to February 2010, the latest M&E surveys took place in eight sentinel schools, bringing the vertical monitoring programme to its 6th year of follow-up. Five of these eight schools had follow-up data available for each year of the study from 2004 to 2010.

Highly reduced levels of *Schistosoma haematobium* intensity were found in all follow-up years as compared to baseline:

Parasite	Stage	Intensity as per model of log-transformed egg count	Percentage change in intensity from baseline	p-value for comparison with baseline
<i>Schistosoma haematobium</i>	Baseline	8.78		
	Follow-up 1	1.19	-86.4	p<0.001
	Follow-up 2	1.06	-87.8	p<0.001
	Follow-up 3	1.45	-83.4	p<0.001
	Follow-up 4	1.96	-77.7	p<0.001
	Follow-up 5	0.61	-93.0	p<0.001

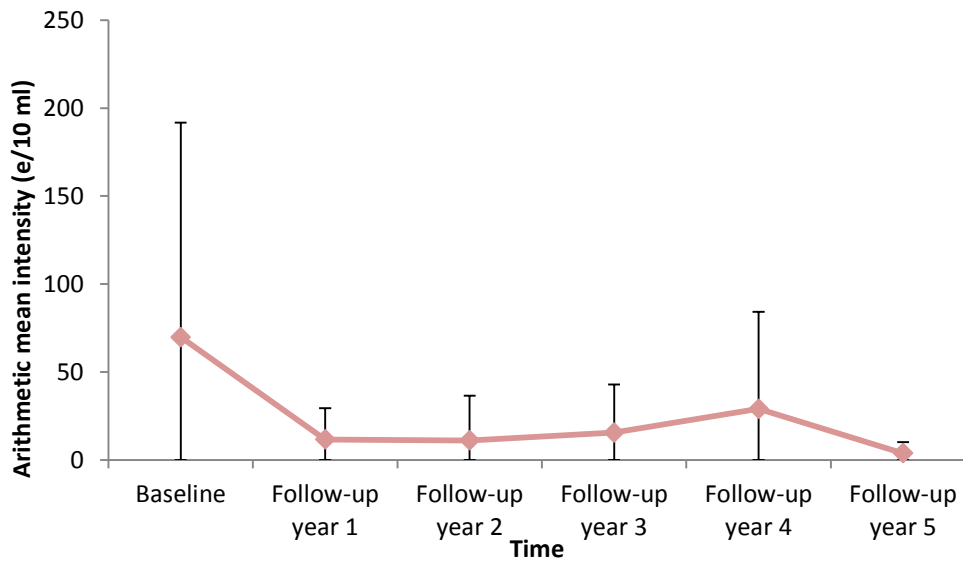


Figure 2. Overall *S. haematobium* arithmetic mean intensity during 6 years of study in Niger (n=433). Error bars are 95% confidence intervals taking into account cluster sampling.

Measures of morbidity were also taken throughout the vertical programme to include: wasting, stunting, anaemia, bladder ultrasonography and upper urinary tract ultrasonography. As an example of a decrease in morbidity that could be attributed to the programme, the following shows the decrease in prevalence of positive global ultrasound scores (a sum of the bladder and upper urinary tract scores) in Tabalak school:

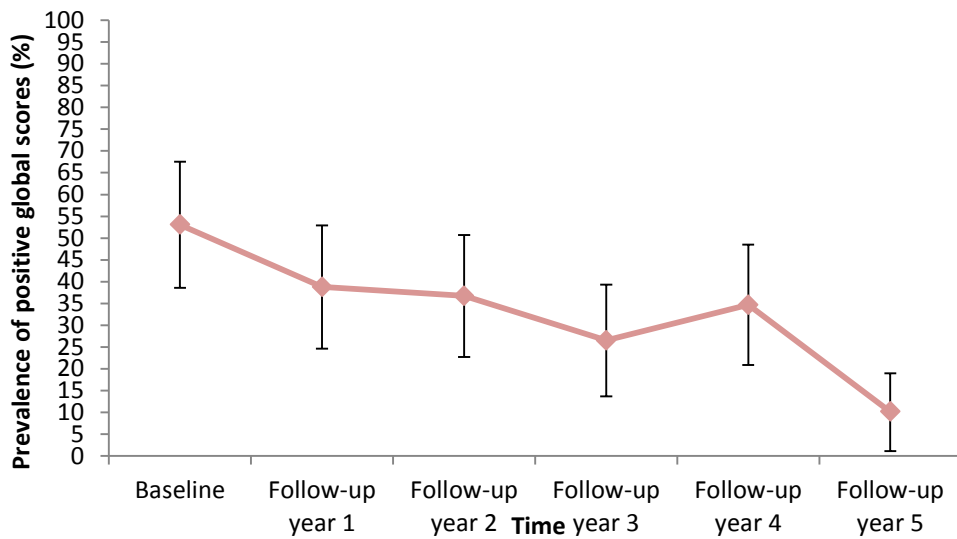


Figure 3. Prevalence of positive global scores for children from Tabalak school during 6 years of study (longitudinal data n =49). Error bars are 95% confidence intervals taking into account cluster sampling.

Niger integrated programme

From 2008, two new schools were surveyed as part of monitoring for the integrated control programme, in which LF and trachoma were treated with ivermectin and azithromycin respectively alongside the existing schistosomiasis treatment program. Measures of trachoma infection were also collected at baseline and for one year of follow-up alongside measurements of prevalence and intensity of schistosomiasis and soil transmitted helminths:

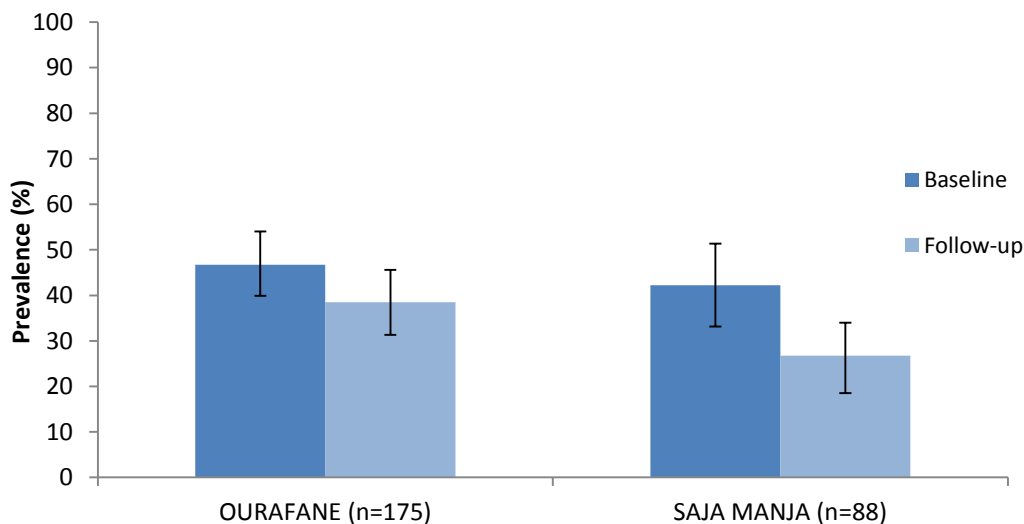


Figure 4. Trachoma prevalence at two schools at baseline and follow-up. Results shown by school for Ourafane and Saja Manja schools. n = 298.

Model results indicate that there was a highly significant reduction in the odds of trachoma infection in children followed up for one year from baseline ($p < 0.01$). Implementation of trachoma control activities is prioritized in communities where the prevalence of active

trachoma in children aged 1–9 years is 10% or higher or where prevalence for people aged 15 years and over is 1% or higher². These results suggest that trachoma control interventions are mandatory in these two districts even after follow-up, despite the significant reduction in trachoma prevalence.

One school at Bonfeba in the Tillaberi region was studied for three years from 2008 in order to monitor the integrated control programme further. In this school, along with Ourafane and Saja Manja, ultrasound data were collected as per the vertical programme. This result serves as an example of a reduction in morbidity being associated with the integrated programme:

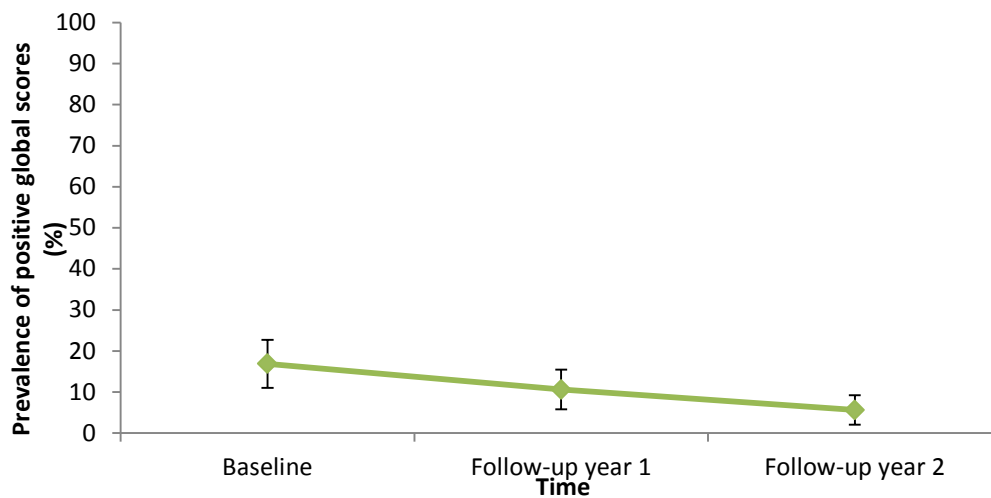


Figure 5. Prevalence of positive global scores during 3 years of study at Bonfeba school. n = 160.

Burkina Faso vertical programme

The annual surveys for the SCI's vertical schistosomiasis control programme in Burkina Faso were carried out from 2004 to 2007 to include three years of follow-up in 19 randomly-selected schools. Treatment was delivered biennially. Final analysis was based on 15 schools as four had at least one whole year of data missing. Highly reduced levels of *S. haematobium* intensity were found in all follow-up years as compared to baseline:

Parasite	Stage	Intensity as per model of log-transformed egg count	Percentage change in intensity from baseline	p-value for comparison with baseline
<i>Schistosoma haematobium</i>	Baseline	8.17		
	Follow-up 1	0.21	-97.5	p<0.001
	Follow-up 2	0.34	-95.9	p<0.001
	Follow-up 3	0.26	-96.8	p<0.001

² Solomon AW, Zondervan M, Kuper H, Buchan JC, Mabey DCW, Foster A. 2006. Trachoma Control: A guide for programme managers. World Health Organisation, Geneva.

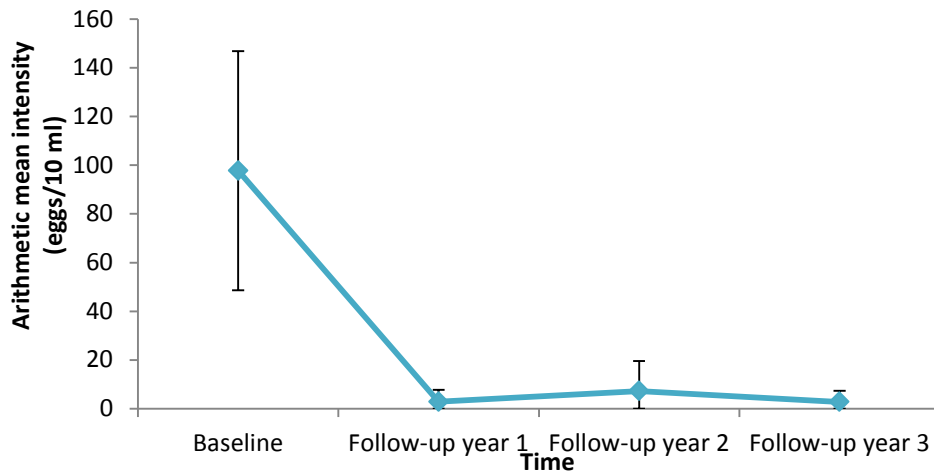


Figure 6. Arithmetic mean intensity of *S. haematobium* infection in Burkina Faso during the vertical program. n = 543. Error bars are 95% confidence intervals taking into account cluster sampling.

Measures of morbidity were also taken throughout the vertical programme to include: wasting, stunting and anaemia. Blood haemoglobin concentration was shown to increase significantly during the course of follow-up:

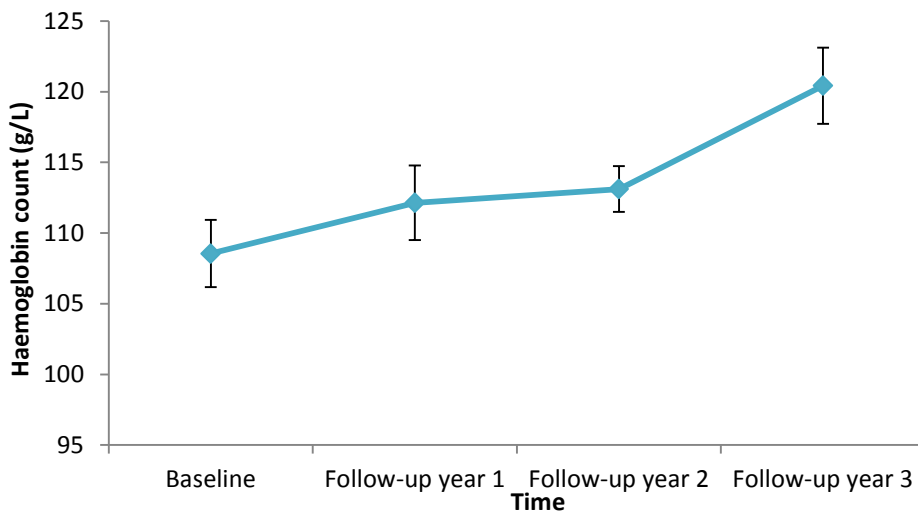


Figure 7. Mean blood haemoglobin concentration in Burkina Faso over 4 years of study. n = 562. Error bars are 95% confidence intervals taking into account cluster sampling.

Burkina Faso integrated programme

The first surveys for the evaluation of the integrated NTD control programme took place in 22 randomly-selected villages (containing a total of 25 schools) in 11 regions in Burkina Faso between November 2007 and February 2008. Children were followed-up for two years after baseline.

Reduced levels of *Schistosoma haematobium* intensity were found in all follow-up years as compared to baseline:

Parasite	Stage	Intensity as per model of log-transformed egg count	Percentage change in intensity from baseline	p-value for comparison with baseline
<i>Schistosoma haematobium</i>	Baseline	0.53		
	Follow-up 1	0.17	-69.0	p<0.001
	Follow-up 2	0.32	-39.6	p<0.001

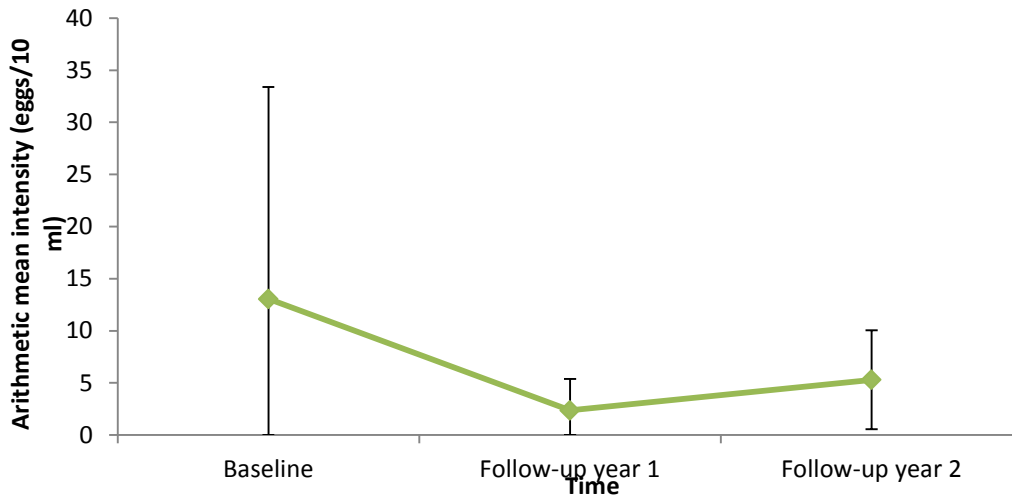


Figure 8. Arithmetic mean intensity of *S. haematobium* infection in Burkina Faso during the integrated program. n = 2188. Error bars are 95% confidence intervals taking into account cluster sampling.

As a means of monitoring nutritional status, height, weight and age were used to calculate the extent of wasting and stunting during the integrated programme. The picture was not as clear-cut as for the parasitological measures; the prevalence of wasting actually increased significantly during the course of the programme and prevalence of stunting reduced slightly:

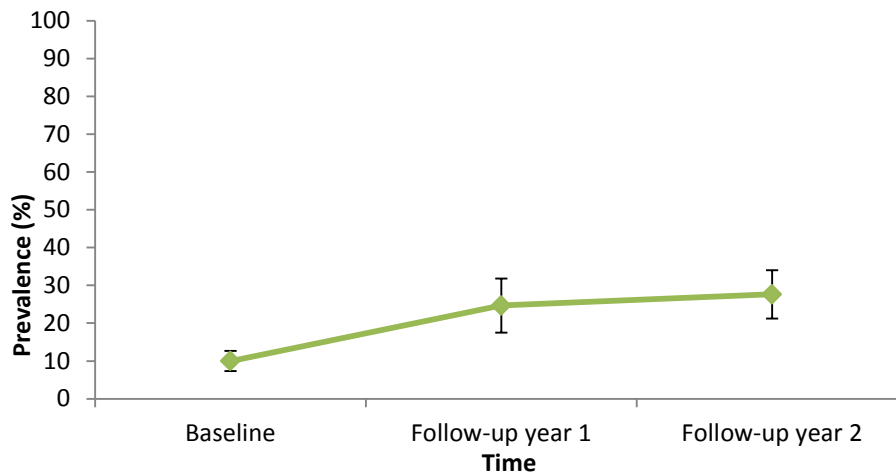


Figure 9. Prevalence of wasting during 3 years of the integrated programmes in Burkina Faso. n = 2405. Error bars are 95% confidence intervals taking into account cluster sampling.

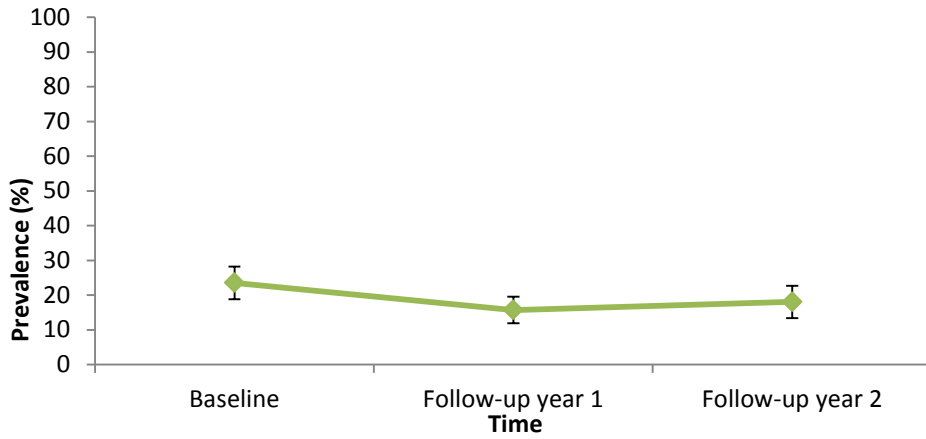


Figure 10. Prevalence of stunting during 3 years of the integrated programmes in Burkina Faso. n = 2405. Error bars are 95% confidence intervals taking into account cluster sampling.

Despite the ambiguous influence of the programme on wasting and stunting, it was associated with a significant increase in blood haemoglobin concentration:

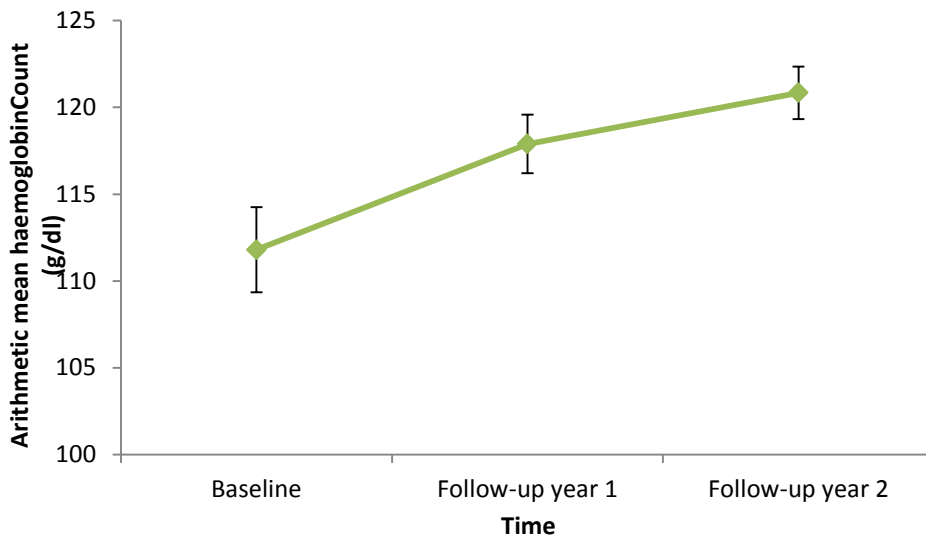


Figure 11. Arithmetic mean blood haemoglobin counts during 3 years of the integrated programme in Burkina Faso. n = 2405. Error bars are 95% confidence intervals taking into account cluster sampling.

Activity 11 Assess impact of integrated control programmes on knowledge, attitudes and practices of decision makers, health care professionals and target populations

In Uganda, SCI staff in collaboration with the Ministry of Health and an economist from Makerere University have conducted in-depth interviews with 48 community medicine distributors (CMDs) across twelve sites to prospectively gather information on the acceptability and accessibility of the NTD control programme. Further focus-group discussions with the CMDs and with communities are currently underway to determine the perceptions of the programme of these primary implementers and beneficiaries and to identify where programme can be developed and improved to their advantage. Key informant interviews with district and sub-district personnel are planned in these areas.

Independent research has also been carried out on local responses to preventive chemotherapy for NTDs in Tanzania and Uganda. This research was carried out by a team of social scientists from the Centre for Research in International Medical Anthropology, Brunel University; the Development Studies Institute, London School of Economics; The National Institute for Medical Research, Tanzania; and the Vector Control Division of the Ministry of Health, Uganda.

This research examined the local level distribution of drugs - both in the community and schools. It documented attitudes to treatment by those providing the drugs and communicating information about the diseases and the treatments being offered. It also assessed modes of delivery and estimated actual take-up and consumption of tablets. Finally, it placed preventive chemotherapy into local social contexts – highlighting the ways in which understandings of the signs and symptoms of NTDs, and affliction more generally, coincided and/or contradicted those associated with biomedicine. Particular attention was paid to how local attitudes changed in response to treatment.

This research has been ongoing since 2005. In Uganda, the main research sites have been Panyimur sub-county, Nebbi district; Wanseko, Buliisa district; and riverine areas of Moyo and Adjumani districts. In Tanzania, research has been undertaken in Ukerewe Island; Mvomero district and Morogoro municipality, Morogoro region; and Muhesa and Pangani districts, Tanga region. Field sites were selected on the basis of high recorded prevalence for at least two NTDs. The primary focus was *S. mansoni* and soil-transmitted helminth infections in Uganda and Ukerewe Island, Tanzania. In Tanga region, Tanzania research initially focussed on *S. haematobium* and soil-transmitted helminth infections, but later involved assessing treatment programmes for LF. In Morogoro region, research focussed on local responses to PCT for *S. haematobium* and onchocerciasis.

Research methods combined participant observation (including observation of drug distribution), checking and investigating details in Ministry of Health registers (including interviewing those involved in the distribution and take-up of drugs), and semi-structured interviews at around 15% of homes in selected villages. A total of 1,500 interviews have been undertaken.

Overall conclusion:

PCT has worked best in schools. In most schools researched, drug take up was high, often exceeding targets. However, PCT in the community, mainly targeted at adults (but also children not attending school), has been less successful. At all the research sites, there has been some resistance to treatment, and modes of tablet distribution have not always been effective. At five sites (Panyimur, Mvomero district, Morogoro municipality, Muhesa and Pangani districts) these problems have been particularly acute, whereas at other sites (Moyo, Ukerewe) they have been somewhat less important and, in one case, largely overcome (Adjumani).

Specific findings:

(1) Considerable variations were recorded between study sites. Divergence was noted in local attitudes towards specific diseases and also between modes of drug delivery and the attitudes of MOH staff and drug distributors. Variation was also noted over time at particular sites.

Understandings of schistosomiasis provide a good example of divergence in local attitudes. *S. haematobium* is commonly perceived as an affliction of childhood (as a frequently reported symptom of infection among young people is red urine) whereas infection with *S. mansoni* does not lead to similarly recognized signs of infection. This directly influences drug take-up, although not necessarily in straightforward ways, as infection with *S. haematobium* may be associated with ideas of pollution and shame and can affect a willingness to take or discuss treatment.

One important finding within 2 of the study sites was that widespread local antipathy to treatment recorded in 2005 had diminished by 2008 due to empirical observations made by local people of what had happened to those that had taken the tablets in 2004 and 2005. This is a factor that helps explain any increased uptake of drugs among adults in subsequent years.

(2) As noted above, mass treatment of children in schools for schistosomiasis and soil-transmitted helminths was found to be successful in terms of the consumption of tablets. In some places, school teachers exceeded the target of treating 75% of registered schoolchildren. (for example, Table 6 shows the uptake of drugs among schoolchildren on Ukerewe Island). The high uptake in schools can be attributed to the lack of agency among children who, with few exceptions, unquestioningly followed the instructions of their teachers.

However, considerable variations were noted in teachers' understandings of the rationale for school-based NTD treatment both within and between study sites. At some locations, for example, the teachers delivering the drugs had been well-informed by Ministry of Health staff about the targeted diseases and the medicines they were giving to their pupils. At other schools, this was not the case. On several occasions, it was observed that the wrong health education materials were used during treatment (i.e. for a different NTD) and on others that neither the pupils nor the teachers themselves understood the information that had been provided.

In some locations, preventive chemotherapy in schools was resisted by children and parents. This occurred in Panyimur at some schools in 2005, following the experience of side effects in 2004. It was also an issue in Morogoro, Tanzania, in 2008, leading to the above mentioned interruption in treatment until the Ministry of Health delivered a clear statement on the benefits of treatment. However, where several repeated treatments have occurred, concerns were found to have lessened. Interviews indicated that this was primarily due to adults making their own empirical observations of how children had benefited from previous rounds of treatment.

(3) There is a tendency for aggregated rates of take up through official channels to be higher than those recorded at the local level. This varies significantly between research sites, between methods of distribution and between NTDs. At one extreme, the distribution of albendazole and ivermectin in Muhesa district, Tanzania was reported by district officials to be '100%' whereas the actual take-up was found to be closer to 25% (a figure derived from data on self-reported uptake and local MoH registers). A more positive example also comes from Tanzania. Data from Ukerewe Island shows that actual take up among schoolchildren was often lower than the rates recorded, but nevertheless higher than the take up target, see Table 6.

School	No of pupils registered	No who took drugs	%	Figures submitted to DSHC	%
Muriti	835	582	70	582	70
Bugula	859	526	61	821	96
Namasabo	907	785	87	785	87
Busumba	730	598	82	712	97
Hamuyebe	945	702	74	702	74
Nansio	864	602	70	864	100
Nakoza	753	589	78	589	78
Kagera	839	591	70	830	99
Buriti	672	437	65	671	99.8
Bwiro	740	582	79	684	92

Table 6. Uptake of praziquantel among school children at selected schools in Ukerewe district, Tanzania during 2007

At most sites, drug take up by adults has never reached the required level during any round of distribution. There are, however, exceptions, such as Adjumani District in Uganda which has shown either consistently high or increasing coverage rates during the several PCT.

(4) Low take up of drugs for NTDs among adults can be attributed to a variety of factors. These vary from one location to another, but fears of side effects and infertility are common. Suspicion of why tablets are given out free without a locally convincing explanation is also prevalent. Other factors include the limited attention given to explaining the rationale for treating adults en masse at most research sites, including adults who are not experiencing symptoms. In Coastal Tanzania, for example, after three rounds of mass treatment for LF, only a very small number of those interviewed were aware that they might be infected, or that mosquitoes are the vector, see Figure 12.

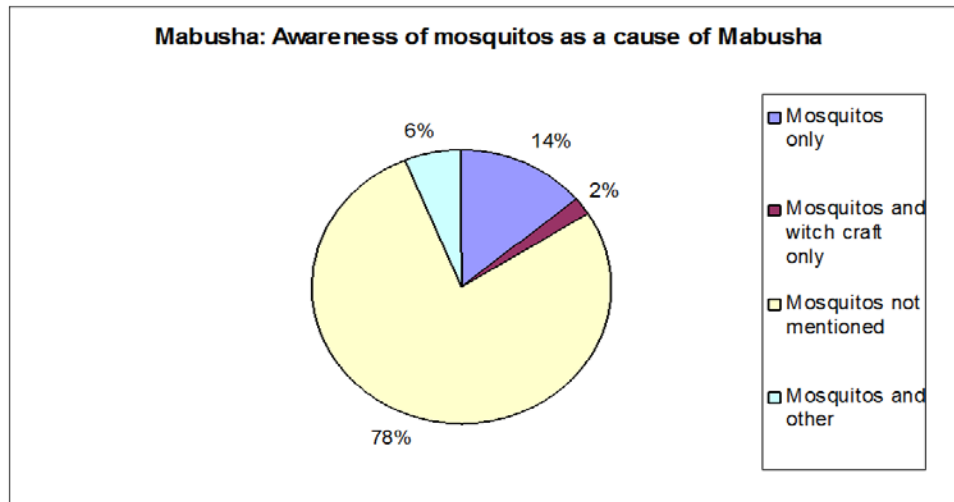


Figure 12: Local understandings of the aetiology of swollen testicles ('mabusha') in Muhesa district, Tanga region: awareness of mosquitoes as a cause of Mabusha.

(5) Finally, it is very important to note that in those places where there have been several rounds of mass treatment for schistosomiasis, the vast majority of adults have taken praziquantel at least once at all selected sites in Uganda (see Table 7). In other words, while many of those interviewed were sceptical about the benefits of being treated repeatedly or were unaware that it might be necessary, those who initially rejected treatment came to recognize that the tablets could have health benefits. Follow-up research was undertaken in Tanzania in 2009 to see if similar trends can be observed and to explore the implications of this for the control of schistosomiasis and other NTDs and the results have been published in the literature³

Treatments	Adjumani (167)		Buliisa (183)		Moyo (107)		Nebbi (108)	
	n	%	n	%	n	%	n	%
Never	8	5	40	22	9	8	5	5
Once or more	159	95	143	78	98	92	102	94
Twice or more	125	75	64	35	57	54	80	74
Three times or more	61	37	13	7	24	23	30	28
Four times or more	20	12	1	1	5	5	3	3

Table 7. Number of times interviewees received PCT between 2004 and 2008. NB PCT occurred in Nebbi in 2004, 2005, 2007 and 2008; in Buliisa in 2005, 2006, 2007 and 2008; in Adjumani in 2006, 2007 and 2008; in Moyo in 2006, 2007 and 2008.

³ See Parker M, Allen T, Hastings J. 2008. Resisting control of neglected tropical diseases: dilemmas in the mass treatment of schistosomiasis and soil-transmitted helminths in north-west Uganda. *J Biosoc Sci.* 40: 161-181.

Parker M, Allen T. 2011. Does mass drug administration for the integrated treatment of neglected tropical diseases really work? Assessing evidence for the control of schistosomiasis and soil-transmitted helminths in Uganda. *Health Systems Research Policy and Systems* 9:3

Allen T, Parker M. 2011. The other diseases of the millennium development goals: rhetoric and reality of free drug distribution to cure the poor's parasites. *Third World Quarterly* 32: 91-117

Molyneux, DH, Malecela MN, 2011. Neglected tropical diseases and the millennium development goals – why the “other diseases” matter: reality versus rhetoric. *Parasites and Vectors* 4:234

Activity 13 Conduct comparative costing analysis between integrated and vertical control programmes

An economic costing protocol and suite of data collection tools became available in March 2008, designed by individuals at Emory University and the Task Force for Child Survival and Development, following successive development meetings of the Gates-funded NTD projects in June and November 2007. Additionally, SCI staff developed a plan for implementing the evaluation in Uganda, Niger and Burkina Faso.

The protocol and tools have been used by SCI staff to collect retrospective (due to when the tools were received) and prospective cost data for the NTD integrated treatment programmes in Uganda (in collaboration with a health economist from Makerere University) and in Niger and Burkina Faso. The results and findings are discussed below.

Uganda

Eleven districts were selected in Uganda using multistage cluster sampling which incorporated potential cost drivers such as NTD drug package, number of drug deliveries and distance from Kampala. In these districts, under the economic evaluation study, Year 1 start up costs, when no integrated NTD treatment occurred, and three subsequent years of data collection were completed. The data have been entered and analysed and the results of the financial costs per person treated are shown in Table 9.

Programme Year	Y2 (2007/8)	Y3 (2008/9)	Y4 (2009/10)
Total cost of delivery	\$2,003,009	\$1,922,159	\$1,581,916
Total cost (inc purchased drugs)	\$2,485,850	\$2,910,808	\$2,355,852
Total cost (inc donated drugs)	\$62,340,200	\$102,376,479	\$131,305,260
Total persons treated for any NTD	8,767,739	14,136,742	13,885,916
Financial cost of delivery per person treated	\$0.23	\$0.14	\$0.11
Economic cost per person treated (inc purchased drugs)	\$0.28	\$0.21	\$0.17
Economic cost per person treated (inc donated drugs)	\$7.11	\$7.24	\$9.46

* prices in US \$

Table 9: Financial costs of NTD treatment in Uganda

These costs per person treated under the integrated strategy are less than those identified by an earlier SCI study⁴ into the cost per schoolchild treated for schistosomiasis and STH control in Uganda. The overall financial cost per child treated in the six study districts was US \$0.39 and the total economic cost per child treated was US\$0.54 (range, \$0.41 to \$0.91), which includes the imputed value of labour as well as annualized capital costs. In addition, the cost per person treated through CDTI for onchocerciasis control in Uganda has been

⁴ Brooker S, Kabatereine NB, Fleming F & Devlin N (2008) Cost and cost-effectiveness of nationwide school-based helminth control in Uganda: intra-country variation and effects of scaling-up. Health, Policy and Planning 23: 24—35;

valued at an average of US \$0.78 (range, \$0.37 to \$2.78)⁵. The costs of the stand-alone Programme for the Elimination of Lymphatic Filariasis in Uganda have still to be analysed to provide a comparison.

Further analysis of the data shows that the cost per person treated is highly sensitive to the total number of persons treated. Increasing the number of persons treated can significantly decrease the cost per person treated which is suggestive of economies of scale. There is significant variation between the cost per person in the districts and an association to the number of deliveries that a community medicine distributor (CMD) has to carry out per PCT round. Further cost-effectiveness and sensitivity analysis are currently being completed which investigate cost by morbidity case averted and estimation of DALYs.

In addition to the costing data carried out in Uganda, a novel method of collecting prospective data, on how CMDs spend their time on NTD and non-NTD related activities, using pictorial diaries was developed and used by 64 CMDs in four of the eleven districts participating in the economic study. The analysis looks at the opportunity costs of the CMD involvement in the NTD control programme and the time-in-motion of the CMDs involvement in NTD activities and measurement of efficiency.

Important outcomes of the study are:

- Additional CMD workload is created when national drug logistics and delivery are untimely which significantly impacts on CMD performance and efficiency.
- Increased workload is also associated with increased 'out-of-pocket' costs for the CMD and thus a financial loss for participating in the programme.
- Analysis by parish shows that treatment coverage is sensitive to the number of days spent distributing the drugs. Decreasing the number of days distributing significantly increases the number of eligible persons being treated.
- The difference in treatment coverage figures between those reported by the districts and those collected through a coverage survey using a cluster sample methodology, where clusters were chosen separately for each drug package (stratum) using population-proportion sampling, were different. The majority of districts significantly over-reported the populations they were treating.

In conclusion:

- CMDs are being undervalued both financially and non-financially following the expansion of NTD control in Uganda
- Affordable programmes with high impact are extremely desirable but high and sustained coverage with community ownership is essential
- Alternative incentive or reward schemes for CMDs need to be developed which are a sound investment for continuity and sustainability

West Africa

Cost analysis was undertaken in Niger for the 2nd and 3rd years of the programme (2008 and 2009), and in Burkina Faso for the 3rd year (2009). Six districts were selected in both Niger and in Burkina Faso through a multistage sampling process which took account of NTD drug packages, deliveries and the distance from the capital. In both countries

⁵ McFarland D et al. unpublished data

programme receipts, district and central drug and treatment records and interviews with accountants and NTD co-ordinators provided information on the capital assets and recurrent and variable resources used and their programmatic costs for the IPCT. A questionnaire on the time spent on campaign activities by government staff provided information for economic costs. In Niger a retrospective questionnaire was administered to 56 staff from different organisational levels. A selection of these people provided views on the campaign and its impact on the health system. In Burkina Faso the same questionnaire was administered to 45 government staff. In addition a questionnaire was administered to community distributors on the time spent on IPCT activities and remuneration. Activity based costing was used to apportion activity related costs by organisation and location. The integrated nature of many activities such as drug transportation, training, organisation and technical support meant these activities were allocated by district, but not by disease. Costs were analysed and reported in constant 2009 terms, and are summarised in Table 10.

	2008		2009		Annualized Cost*	
	US\$ 6 districts	\$/100,000 treatments	US\$ 6 districts	\$/100,000 treatments	US\$ 6 districts	\$/100,000 treatments
Programme expenditure						
Capital	5,916		2,104		4,038	
Recurrent	38,074		26,767		32,504	
Variable	295,650		289,125		292,436	
Total Programme	339,641	10,300	317,996	7,967	328,978	9,040
International tech. support	49,227		41,147		45,247	
Government /opportunity cost	282,036		322,700		302,068	
Drug cost	12,908,999	391,499	13,607,861	340,930	13,253,266	364,178
Total Economic Cost	13,579,902	411,846	14,289,704	358,013	13,929,558	382,761

* Annualized cost or average annual cost of discounted values

Table 10. Economic and financial costs of integrated control in Niger (2009 constant prices)

In Burkina Faso the programme cost for the 6 districts was \$262,239, the drug cost was \$10,212,595 and the total economic cost was \$10,850,684. A total of 2,913,389 treatments were delivered in the 6 districts at an average programmatic cost per person of \$0.09, an economic cost per person of \$3.72 including the average drug cost of \$3.51 per person.

Unlike other countries Burkina Faso data activity and reporting allowed costs to be apportioned by disease. The average economic cost per treatment for trachoma, LF, and schistosomiasis is estimated as \$0.22, \$0.20 and \$0.26 respectively. The average financial cost per treatment for the same diseases is \$0.10, \$0.08 and \$0.12 respectively. These can be compared with the vertical programme costs shown in Table 11. Further information on the costs of the vertical programmes is available in peer reviewed publications⁶.

⁶ Gabrielli AF, Touré S, Sellin B et al. (2006). A combined school- and community-based campaign targeting all school-age children of Burkina Faso against schistosomiasis and soil-transmitted helminthiasis: performance, financial costs and implications for sustainability. Acta Trop 99:234-42

And

Country /Disease	LF	Schistosomiasis	Trachoma
Niger	Not treated	\$0.135*	\$0.15~
Burkina Faso	\$0.14	\$0.11	Not treated

* including international technical and management costs excluding mapping, sentinel monitoring costs

~ national costs only excluding government salaries

Table 11. Vertical programmatic costs of treatment in Burkina Faso (2009 constant prices)

Comparison of vertical and integrated costs

The comparison between costs from vertical and integrated programmes is complicated by a number of factors. These include:

- Learning effects: the integrated programmes benefit from previous learning and planning experiences, allowing, for example, shorter training courses; and more rapid scale up;
- Scale economies: the budget available to the integrated programmes was greater than that available to the combined vertical programmes. Scale economies are in part due to funding as well as savings in the integrated nature of the programme;
- Introduction of additional programmes (LF in Niger and trachoma in Burkina Faso) which increased the numbers of treatments reducing costs per treatment for the integrated programme;
- The number of drug modules delivered per district is a key driver in the cost savings and these are particularly affected by the introduction of new programmes and the objectives of the vertical and integrated programmes. Vertical programmes generally tackled areas with high burdens of disease, whereas integrated programmes faced a number of compromises in selecting and prioritising districts to be treated.
- Cost per DALY averted is potentially a more robust measure of effectiveness. However the metric is complicated, not only by additional data requirements but by the debate on NTD DALY weights. The most prominent being that on the inclusion of chronic morbidities resulting from STH and schistosomiasis.

These points are further raised by Leslie et al, in Prep.⁷

Leslie J, Garba A, Oliva EB, et al. (2011) Schistosomiasis and Soil-Transmitted Helminth Control in Niger: Cost Effectiveness of School Based and Community Distributed Mass Drug Administration. PLoS Negl Trop Dis 5(10): e1326. doi:10.1371/journal.pntd.0001326

⁷ Leslie J, Garba A, Kadri B, et al. In Prep. Integrated control of neglected tropical disease in Niger: How do the costs compare with vertical control?

Activity 14 Utilise statistical and mathematical modelling techniques to quantify and evaluate different treatment strategies and relate these to health indicators and cost analysis (baseline data used to prepare predictive model)

Background

In the past decade there has been significant progress in the momentum of control programmes against schistosomiasis, and in many areas the primary objectives of reducing infection intensity, prevalence, and associated morbidity have been achieved. However, given the robustness of helminth infections to control perturbations and in the absence of more permanent control interventions such as water and sanitation improvements and snail clearance, infection levels will likely return towards endemic equilibrium.

Previous modelling work at the SCI has quantified changes in the level of transmission associated with PCT, and suggests that for both *S. mansoni* and *S. haematobium*, significant and substantial reductions in transmission are observed following successive rounds of praziquantel treatment, even in areas with high underlying endemicity. Although the greatest reductions are seen in treated individuals, there are also clear benefits to those individuals who have not received treatment (French et al, 2010⁸; French et al, in Prep⁹). These results have been validated using the extensive SCI datasets which contain observations from individuals both pre and post multiple rounds of treatment; and to our knowledge this is the first time this has been done on such a scale.

Understanding these changes in transmission is crucial to be able to project the future infection situation under different treatment scenarios. For both species of schistosome in many geographic locations there has been a reduction in infection prevalence to well below 10%. More importantly from a morbidity control programme, the infection intensity has also been subdued to low levels, as this is thought to be a more reliable proxy of the probability of developing morbidity.

Here we further develop those models in order to compare different treatment approaches, in terms of treatment frequency and target populations, in areas where measures of parasite abundance have already been suppressed. Given that large-scale improvements in water and sanitation is not currently a major control strategy (although we note recent trials to quantify their expected benefit) and lasting changes to health behaviour have, to-date, been difficult to achieve, here we explore the projected impact of different praziquantel treatment scenarios.

⁸ French MD, Churcher TS, Gambhir M, Fenwick A, Webster JP, Kabatereine NB, Basáñez M-G. 2010. Observed reductions in *Schistosoma mansoni* transmission from large-scale administration of praziquantel in Uganda: a mathematical modelling study. PLoS Negl Trop Dis 4: e897

⁹ French MD, Churcher TS, Gambhir M, Fenwick A, Webster JP, Kabatereine NB, Basáñez M-G. In Prep. Estimation of changes in the force of infection for intestinal and urogenital schistosomiasis in countries with Schistosomiasis Control Initiative-assisted programmes.

Modelling Approach

A mathematical model describing the change in mean infection intensity over time in a population of human hosts has previously been developed for both *S. mansoni* and *S. haematobium*. A fuller description of the model is outlined in Appendix 4.

This model was fitted to longitudinal cohort datasets of school-aged children who were followed up annually across up to three treatment years. In the current analysis the models were then developed further to project forward the likely change in the mean intensity of the infection in the whole community (including treated and untreated individuals) where the level of treatment coverage was allowed to vary for school-aged children and adults.

This was done separately for areas of differing endemicity at baseline for both *S. mansoni* and *S. haematobium* (*S. mansoni*: High ≥ 400 eggs per gram of faeces [epg]; Medium 100-399 epg; Low 1-99 epg. *S. haematobium*: High ≥ 50 eggs per 10ml urine [e/10ml]; Low 1-49 e/10ml). Different treatment approaches were also assumed and projected forward (Annual; biennial; triennial treatment, and treatment cessation).

For both *S. mansoni* and *S. haematobium* the future rebound of the force of infection (FOI – the rate at which hosts acquire parasites), and subsequent parasite intensity was then projected, assuming a saturating function of the FOI back to the baseline value (see Appendix 4 for details).

Treatment coverage assumptions

In the longitudinal cohort to which the models were initially fitted, 100% coverage was assumed in those children that were followed up across all years. However when translating this to the likely impact in the wider community, the following treatment coverage figures were assumed:

- School-aged children: In all areas, coverage of school-aged children was assumed to be 75%, generally in line with estimates from the field (Fenwick et al., 2009¹⁰)
- Pre-school-aged children: It was assumed that there was no treatment of young children (≤ 6 years).
- Adults:
High Intensity Areas: 50%
Medium Intensity Areas (*S. mansoni* only): 20%
Low Intensity Areas: 0%

Country Datasets Used:

In the current analysis, modelling work was conducted on the cohorts from Uganda and Burkina Faso as illustrative examples. The countries provided the most extensive datasets for *S. mansoni* and *S. haematobium* respectively.

Uganda: This was the first of the SCI-assisted programmes to implement a large-scale control programme, commencing in 2003, predominantly against *S. mansoni*. Here we take as a baseline the situation as of 2006, following 3 annual rounds of

¹⁰ Fenwick A, Webster JP, Bosqué-Oliva E et al. 2009. The Schistosomiasis Control Initiative (SCI): rationale, development and implementation from 2002-2008. Parasitology 136: 1719-1730.

schistosomiasis control. The reduction in infection markers in the treated cohort has been reported elsewhere (Kabaterine et al, 2007¹¹).

Burkina Faso: Providing a dataset for *S. haematobium*, Burkina Faso was treated in years 2004 and 2006 (2005 was a treatment holiday). Here we take as a baseline the situation at 2006, following 2 rounds of schistosomiasis control (Koukounari et al, 2007¹²).

Results and Discussion

The projected changes in the mean infection intensity following a range of treatment frequencies are displayed in Figure 13 (*S. mansoni* in panels a-c, *S. haematobium* in panels d-e). For *S. mansoni*, continued yearly treatment is projected to keep infection levels suppressed in high intensity areas and further depress them in medium and low intensity areas. Biennial treatment is projected to be sufficient to keep levels suppressed in most areas, but triennial treatment is not expected to be sufficient in high intensity areas. Treatment cessation will, as expected, result in the rapid bounce back of infection towards endemic equilibrium. Sensitivity analyses around these results (not shown) suggest that the speed of this bounce-back relies heavily on the mean life-span of the parasite assumed (here taken as 4 years). However, we take this opportunity to state that even where there is treatment cessation, there will still be a benefit accrued to those individuals who received treatment, via a reduced probability of developing later sequelae. Similar results are observed for *S. haematobium* infection (panels d and e).

The modelling results presented here are estimated at a relatively macro-scale; that of the area of endemicity. However, there is likely to be great heterogeneity between transmission areas as schistosomiasis is fundamentally a very focal disease. Results will likely depend on the schistosome species, location and time-point under study, and so caution is advised when extrapolating such results too widely. This is examined further in an upcoming publication (French et al, In Prep).

As outlined in the methods above, the differing intensity areas have different assumptions about treatment coverage of adults. The implications of this are that further rounds of annual treatment in high (and medium for *S. mansoni*) intensity areas result in infection levels staying suppressed to their current level. However in low intensity areas further suppression of infection is observed, potentially towards (as yet unidentified) transmission breakpoints. This raises the question of whether continued treatment alone may be sufficient to push infection to local elimination in such places. To explore this, a range of treatment coverages of adults were examined in a low intensity setting (using *S. haematobium* in Burkina Faso as an example; Figure 14). Currently it is assumed that no adults are treated in such low intensity settings. However modelling varying levels of adult coverage resulted in the average parasite levels being further depressed.

¹¹ Kabaterine NB, Brooker S, Koukounari A et al. 2007. Impact of a national helminth control programme on infection and morbidity in Ugandan schoolchildren. Bull WHO 85: 91-99

¹² Koukounari A, Gabrielli AF, Touré S et al. 2007. *Schistosoma haematobium* infection and morbidity before and after large-scale administration of praziquantel in Burkina Faso. J Infect Dis 196: 659-669.

Where treatment coverage of adults is high the mean intensity of infection is projected to fall to very low levels; below one worm per person in many cases. Under such circumstances, and where treatment of young children is proposed (these current models assume no treatment under 6 years), then local elimination of infection may be possible. However, given the overdispersed nature of the parasite, the mean intensity required before approaching the transmission breakpoint are typically thought to be significantly lower than one per person. As parasites become more concentrated in a subset of heavily infected hosts, the mating probability of the parasite will need to be incorporated into the model structure and will become increasingly influential at low levels: here the probability of a host having a single-sex infection of parasites becomes non-negligible. When exploring the likelihood of elimination then the use of such deterministic models as developed here become less useful. The development of a stochastic class of model will be required, that better capture the chance infection events occurring at low intensity levels. Such models will also need to incorporate the focality of infection, the inter-connectedness of transmission areas, and other control options (water and sanitation improvement, snail control). This is an area that the SCI is hoping to develop in the future, supported by other funding sources, but building on the work developed under the BMGF grant.

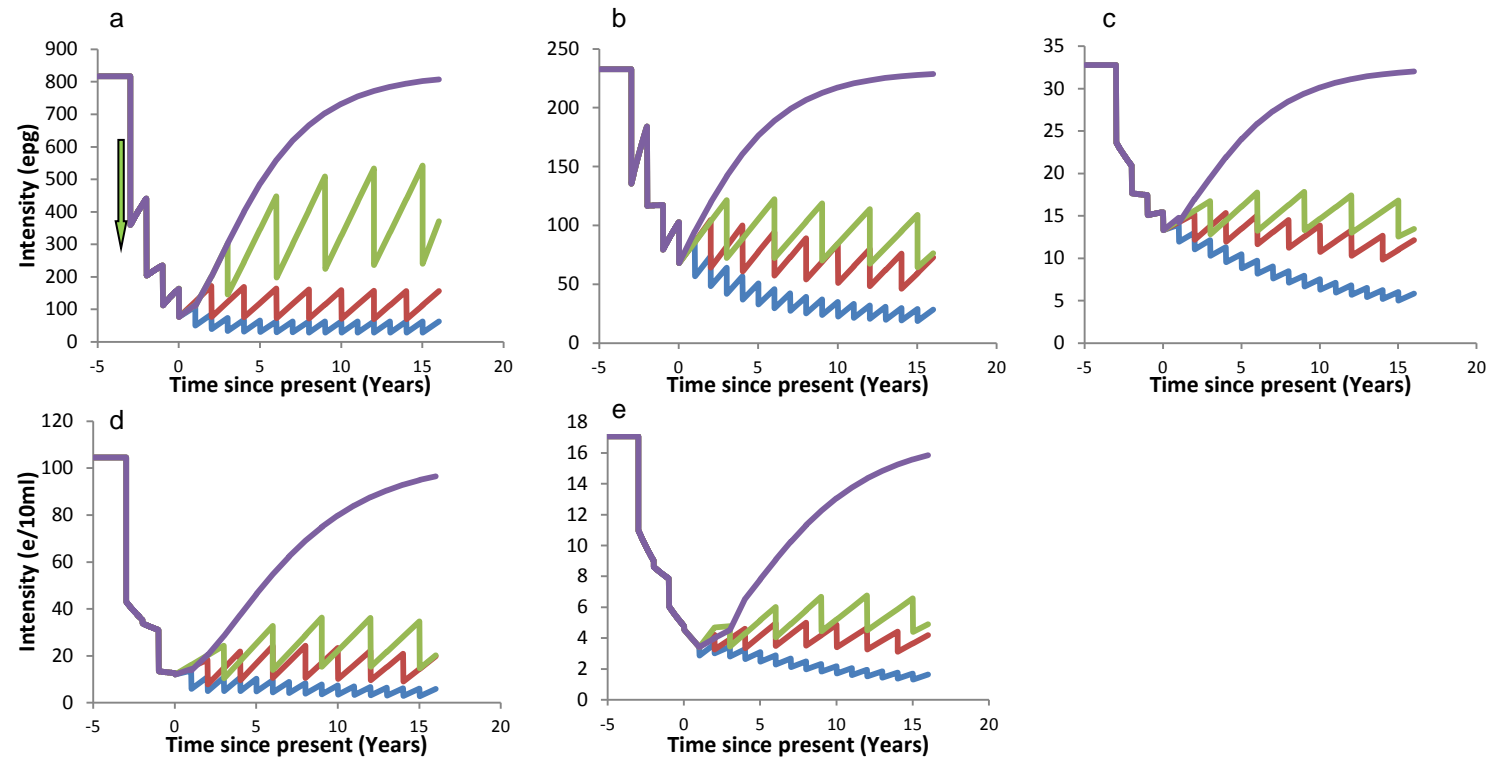


Figure 13. The impact of differing treatment regimes on the average intensity of schistosome infection. The baseline situation is taken following three rounds of treatment (time point 0, marked by green arrow). Blue line indicates continued yearly treatment, red line indicates biennial treatment, green line indicates triennial treatment, and purple line treatment cessation. For a) *S. mansoni* in Uganda High Intensity areas (≥ 400 eggs per gram of faeces [epg]); b) *S. mansoni* in Uganda Medium Intensity areas (100-399 epg); c) *S. mansoni* in Uganda Low intensity areas (1-99 epg); d) *S. haematobium* in Burkina Faso High Intensity areas (≥ 50 eggs per 10ml urine [e/10ml]); and e) *S. haematobium* in Burkina Faso Low Intensity areas (1-49 e/10ml). In all areas, future treatment coverage in school-aged children is assumed to be 75%. Treatment coverage of adults is assumed to be 50% in high intensity areas, 20% in medium intensity areas, and 0% in low intensity areas. No treatment of pre-school-aged children is assumed.

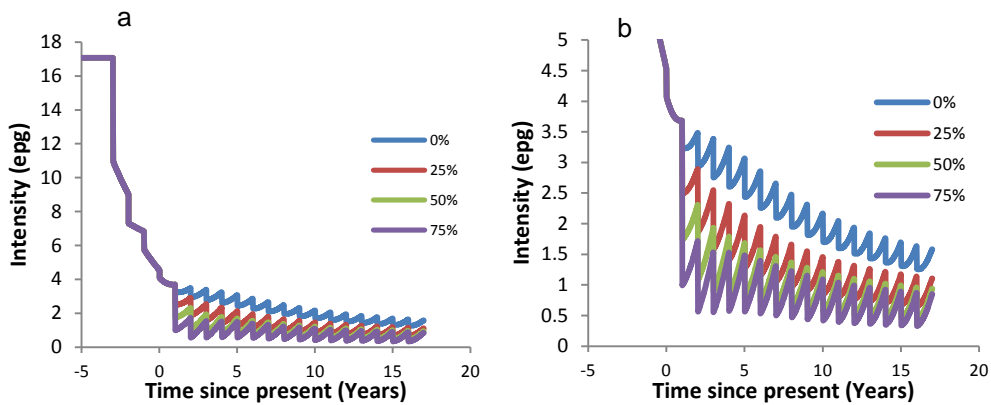


Figure 14. Impact of altering coverage of adults in ongoing yearly treatment schedule in low intensity settings for *S. haematobium* in Burkina Faso. a) Shows full time line, and b) shows detail. Blue line indicates 0% coverage of adults; red line 25% coverage of adults; green line 50% coverage; purple line 75% coverage. All scenarios assume continued 75% coverage of school-aged children and no treatment of pre-school-aged children.

The modelling work presented here, and that proposed in the short-to-medium term future will assist with the transition of control programmes from the initial “active phase” to a “consolidation phase”, or even to identify where elimination may be possible in a given location. Such models will be useful to help governments of endemic countries plan for the future treatment needs in country, as well as helping to inform the global requirements of praziquantel in the medium term.

This modelling work will be validated with further monitoring and evaluation data collected in the field, and is currently being prepared for publication.

Appendix 4: Further modelling details pertaining to Activity 14

Models were constructed in the software Berkeley Madonna.

Model Structure

Full details of the population dynamics model for *S. mansoni* can be found in French et al. (2010) and in the supplementary information of that paper. The rate of change in mean adult worm burden (M) (after the conversion from egg output to adult female burden of 5.26 epg per mated female worm for *S. mansoni* and 3.90 for *S. haematobium*) with respect to host age (a) and time (t) can be described by the following immigration-death equation,

$$\frac{\partial M(a,t)}{\partial t} + \frac{\partial M(a,t)\partial a}{\partial t} = \Lambda(a) - \mu_M M(a,t) \quad [1]$$

where $\Lambda(a)$ is the net *FOI* at age a , and μ_M is the per worm death rate of established adult worms. In turn, $\Lambda(a)$ is given by Equation 2,

$$\Lambda(a) = \lambda_B \zeta_P \tau(a). \quad [2]$$

Here, λ_B is the average underlying baseline *FOI* per person, ζ_P is the relative to baseline ratio of the average *FOI* after each round of treatment, with subscript P indicating the number of rounds of praziquantel treatments received, and the function $\tau(a)$ describes the (dimensionless) age-specific contact function normalized over the total host population.

The return of the *FOI* following treatment is assumed to follow as saturating function, described by:

$$\zeta(t) = 1 - e^{-\beta t} \quad [3]$$

where $\zeta(t)$ is the *FOI* at time t , as a proportion of the baseline level, and β determines the rate of return. Figure 1A shows examples of the return of the *FOI* given varying levels of β .

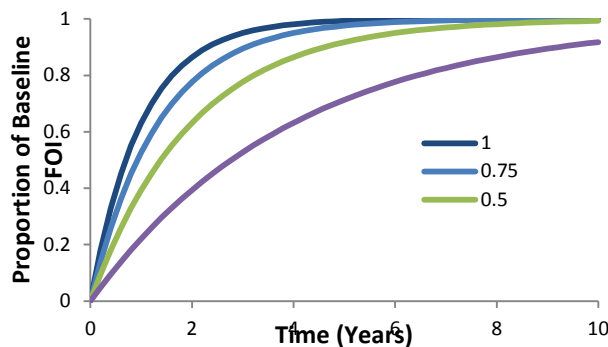


Figure A1. The rebound in the *FOI* back towards baseline levels given by equation 3 assuming values of β as shown in the legend