VOLUME 19 NO 6 PP 706–718 JUNE 2014

Impact of periodic selective mebendazole treatment on soil-transmitted helminth infections in Cuban schoolchildren

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Abstract

OBJECTIVE To evaluate the impact of periodic selective treatment with 500 mg mebendazole on soil-transmitted helminth (STH) infections in Cuban schoolchildren.

METHODS We followed up a cohort of 268 STH-positive schoolchildren, aged 5–14 years at baseline, at six-month intervals for two years and a final follow-up after three years. Kato-Katz stool examination was used to detect infections with *Ascaris lumbricoides*, *Trichuris trichiura* and hookworm. Common risk factors related to STHs were assessed by parental questionnaire.

RESULTS A significant reduction in the number of STH infections was obtained after three years with the highest reduction for *T. trichiura* (87.8%) and the lowest for hookworm (57.9%). After six months, cure rates (CRs) were 76.9% for *A. lumbricoides*, 67.4% for *T. trichiura* and 44.4% for hookworm. After two treatment rounds, more than 75% of all STH-positive children at baseline were cured, but with important differences between STH species (95.2% for *A. lumbricoides*, 80.5% for *T. trichiura* and 76.5% for hookworm). At the end of the study, these cumulative CRs were almost 100% for all three STHs. Risk factors for STHs were sex, sanitary disposal and habit of playing in the soil.

CONCLUSIONS Our results indicate that periodic selective treatment with 500 mg mebendazole is effective in reducing the number of STH infections in Cuban schoolchildren. Although important differences were found between helminth species, two rounds of treatment appeared sufficient to obtain substantial reductions.

keywords Cuba, effectiveness, mebendazole, schoolchildren, selective treatment, soil-transmitted helminths

Introduction

Soil-transmitted helminths (STHs), that is, *Ascaris lumbricoides*, *Trichuris trichiura* and hookworm, are among the most common parasitic infections worldwide (Awasthi *et al.* 2003; de Silva *et al.* 2003; Hotez *et al.* 2006) and especially prevalent in the tropics and subtropics (de Silva *et al.* 2003; Bethony *et al.* 2006). They affect more than two billion people and mostly school-age children (Awasthi *et al.* 2003; de Silva *et al.* 2003; Bethony *et al.* 2006; Hotez *et al.* 2006). Many individuals living in endemic areas are infected continuously from soon after birth throughout childhood (Awasthi *et al.* 2003; Hotez *et al.* 2006). STHs are intimately related with poverty, poor sanitation and lack of clean water, but other risk factors have also been identified (Montresor *et al.* 1998; de Silva *et al.* 2003; Bethony *et al.* 2006; Hotez *et al.* 2006). Although light infections are often asymptomatic, heavy infections can cause a range of morbidities, including anaemia, impaired nutritional status and delayed physical and cognitive development (Awasthi *et al.* 2003; Bethony *et al.* 2006; Hotez *et al.* 2006).

Periodic anthelminthic treatment with single dose, broad-spectrum drugs targeted at schoolchildren is considered one of the most cost-effective strategies to control helminth infections in endemic areas (Montresor *et al.* 2002; Hotez *et al.* 2006) and is endorsed by WHO (WHO 2002, 2005, 2006). Mass treatment (i.e. irrespective of infectious status) of all schoolchildren is recommended either biannually in high endemic areas with

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prevalence of at least 50% or annually in moderate endemic areas with prevalence of 20–49%. Selective treatment (i.e. administered individually based on either diagnosis or suspicion of current infection) is recommended in low endemic areas with prevalence below 20% (Hotez *et al.* 2006; WHO 2006).

Four anthelminthics are currently on the WHO list of essential medicines for the treatment and control of STHs: albendazole, mebendazole, levamisole and pyrantel (WHO 2011a,b). Albendazole (200 or 400 mg) and mebendazole (500 mg) are recommended by WHO as they can be administered as a single dose to all children over 12 months old (Montresor *et al.* 2003; WHO 2006). Both drugs are effective, well tolerated and inexpensive (WHO 2002; de Silva *et al.* 2003; Hotez *et al.* 2006).

The efficacy of these anthelminthics has mainly been investigated by randomised controlled trials (RCTs). A meta-analysis of RCTs showed that the cure rates (CRs) of albendazole and mebendazole are high for *A. lumbricoides*, and unsatisfactory for *T. trichiura*. For hookworm, cure rates of mebendazole are unsatisfactory, while albendazole gives better results (Keiser & Utzinger 2008).

Various papers report on the effectiveness of periodic anthelminthic treatment, but mainly in the context of (targeted) mass treatment studies (Bundy *et al.* 1990; Albonico *et al.* 1996; Fernando *et al.* 2001; Idris *et al.* 2001; Fallah *et al.* 2002; Beltramino *et al.* 2003; Sinuon *et al.* 2003; Saathoff *et al.* 2004; Zhang *et al.* 2007; Waikagul *et al.* 2008; Massa *et al.* 2009; Stothard *et al.* 2009). Only few studies exist on the impact of periodic selective treatment (Curtale 1995; Taylor *et al.* 1995; Beltramino *et al.* 2003). Nevertheless, many areas with low endemicity for STHs – and thus target areas for selective treatment – exist, especially in Latin America and Asia. Moreover, in view of the ongoing mass deworming campaigns in Africa (Fenwick 2006; Kabatereine *et al.* 2006), many currently high endemic areas are expected to become less endemic, involving a shift from mass treatment towards selective treatment strategies. Therefore, more information about the effectiveness of selective anthelminthic treatment is timely and essential.

In this study, we evaluated the impact of periodic selective mebendazole (500 mg) treatment on STH infections in Cuban schoolchildren under field conditions during a follow-up period of three years.

Methods

Study design and population

A longitudinal study was performed in primary schoolchildren, aged 5–14 at baseline, in San Juan y Martínez (SJM) and Fomento, two Cuban municipalities. Both municipalities are in rural mountainous areas, that is, Pinar del Rio, a province in the west of Cuba, and Sancti Spiritus, a province in the centre of the island, which are known to be endemic for STHs (Fajardo Toledo *et al.* 1978; Escobedo *et al.* 2007). Reported prevalence in SJM and Fomento was 24% and 18%, respectively (Wordemann *et al.* 2006). In SJM, the study was started in December 2003–January 2004 and was completed in February–March 2007, while in Fomento, the study was started in May 2004 and ended in April–May 2007 (see Figure 1).

Rural and urban primary schools were randomly selected from SJM ($n = 5$) and Fomento ($n = 14$). All STH-positive children were included in the study at baseline [period 0 (P0)], that is, 107 children from SJM and 161 children from Fomento. They were followed up 6 months (P1), 12 months (P2), 18 months (P3), 24 months (P4) and 36 months (P5) after baseline. The study was performed as part of a larger study; further details have been described previously (Wordemann *et al.* 2006, 2008).

Ethics statement

Written informed consent was obtained from the parents or guardians of each participating child. The study was approved by the Ethical Committees of the Institute of Tropical Medicine in Antwerp, Belgium, the National Institute for Hygiene, Epidemiology and Microbiology, and the Pedro Kourí Institute of Tropical Medicine in Havana, Cuba.

Infection and treatment

From each child, one fresh stool sample was collected at the different measurement periods. Each stool sample was examined by a duplicate Kato-Katz smear (2×25 mg = 50 mg) according to standard procedures to detect *A. lumbricoides*, *T. trichiura* and/or hookworm (*Necator americanus* and *Ancylostoma duodenale*) (Katz *et al.* 1972; WHO 1991; Polderman 2005). Infection intensity was expressed as eggs per gram of faeces (epg). At each measurement period, STH-positive children received one single dose of 500 mg mebendazole which is evaluated and the treatment of choice in Cuba (Nuñez Fernández *et al.* 1989), and in accordance with WHO guidelines (Montresor *et al.* 2002).

Infection risk factors

Common risk factors for parasitic infections, as described in literature (Montresor *et al.* 1998; de Silva *et al.* 2003;

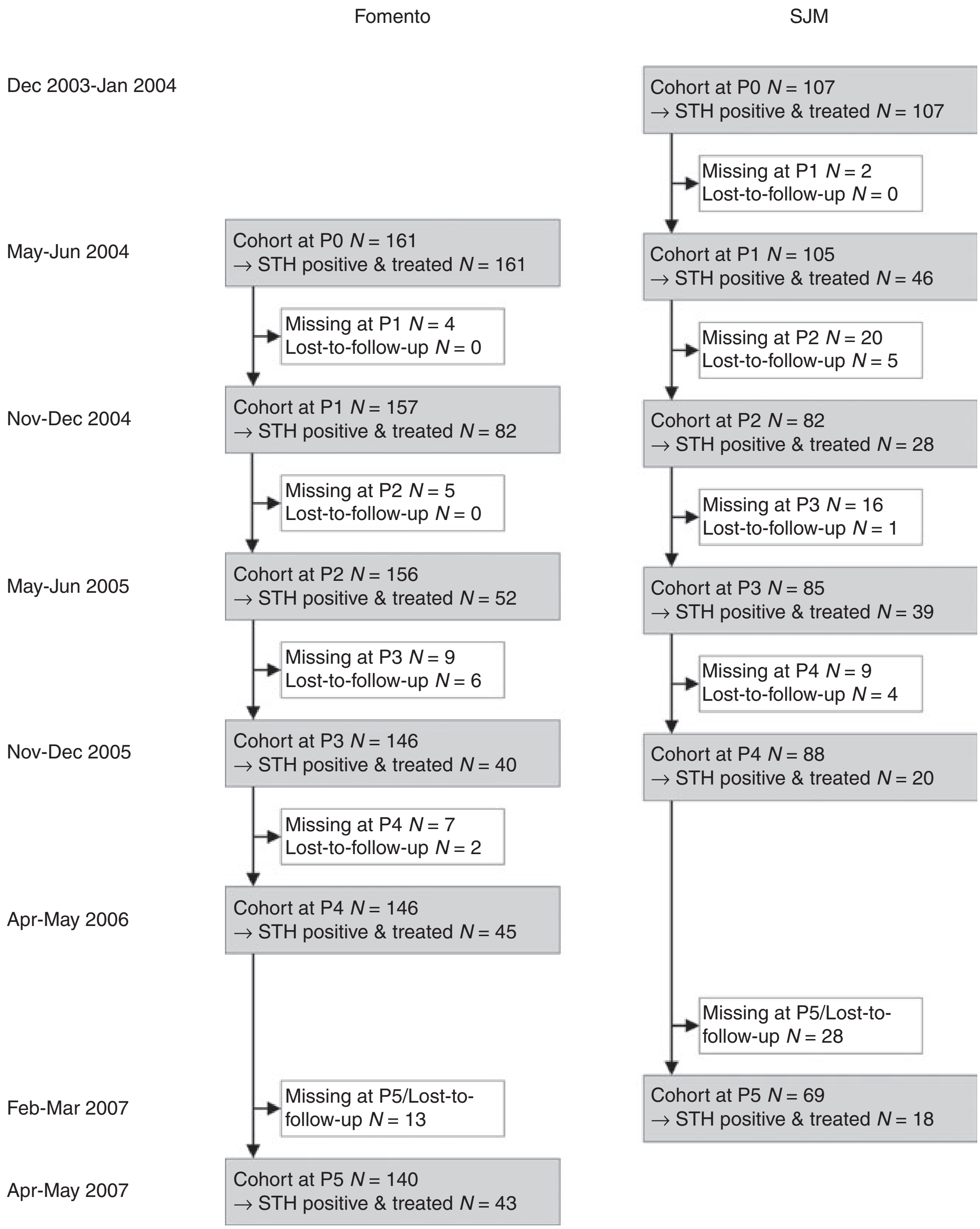

Figure 1 Flow diagram of the study.

Traub *et al.* 2004; Bethony *et al.* 2006; Hotez *et al.* 2006; Wordemann *et al.* 2006), were assessed by parental questionnaire for all participating children. Questions on demographic/environmental risk factors were related to age (years), sex, living area (rural *vs.* urban) and municipality (SJM *vs.* Fomento); those on socioeconomic risk factors to household income (≤250 pesos (≈7 euro)/month *vs.* > 250 pesos/month) and education level of the parents [<12 grades (≈high school) *vs.* ≥ grade 12]; those on sanitary risk factors to water supply (piped water *vs.*

well or river) and sanitary disposal (toilet *vs.* latrine or open-air defaecation); and those on living conditions to crowding (≤2 persons/bedroom *vs.* >2 persons/bedroom). Behavioural habits were drinking unboiled water (yes or no), eating with unwashed hands (yes or no), eating unpeeled/unwashed fruits or unwashed vegetables (yes or no), playing in the soil (yes or no), biting fingernails/sucking thumb (yes or no) and walking barefoot (yes or no).

Statistical analysis

All statistical analyses were performed with SPSS Statistics 17.0 for Windows (SPSS Inc., Chicago, IL, USA), and a *P*-value of ≤0.05 was considered as statistically significant. Differences in parameters between measurements points were assessed by the McNemar test and between municipalities by the chi-square test for nominal variables and Student's *t*-test for scale variables.

Infection was described by percentage of STH-positive children for each STH species, cumulative percentage of children positive for at least one STH infection, percentage of children infected with multiple infections (i.e. at least two STH species simultaneously), infection intensity expressed as the geometric mean (GM) of the epg in infected children and percentages of STH-positive children having a light, moderate or heavy intensity infection according to the WHO classification (Montresor *et al.* 1998). The following indices were used to investigate the impact of treatment:

- Prevalence reduction rates (PRRs), that is, percentage reduction in STH prevalence after treatment, between two (consecutive) measurement periods were calculated as [1 - (prevalence after treatment/prevalence before treatment)]*100%; calculated irrespectively of the presence of the same children at both periods.
- Cure rates (CRs), that is, percentage of STH-positive children found to be STH negative after treatment, between two (consecutive) measurement periods were calculated as [1 - (# positives after treatment/# positives before treatment)]*100%; calculated only in children present at both periods.
- Cumulative cure rates (CCRs), that is, the total percentage of STH-positive children at baseline cured after multiple rounds of treatment, were calculated from baseline till three years of periodic treatment.
- Egg reduction rates (ERRs), that is, percentage reduction in GM epg after treatment, between two (consecutive) measurement periods were calculated as [1 - (GM epg after treatment/GM epg before treatment)]*100%.

Potential risk factors for 'persistent' STH infections were investigated by comparing two extreme groups of children with any STH infection. One group consisted of those children who during the study period were infected and subsequently treated only once, that is, 'non-persistent infection' (n = 84). The other group consisted of those children who were infected and subsequently treated 4–5 times, that is, 'persistent' infection (n = 54) (including possible treatment failure and reinfection). Univariate logistic regression analyses were conducted to assess the relationship of each potential risk factor with the outcome measure separately. Subsequently, all risk factors were entered into a multivariable logistic regression model to develop a prediction model by performing backward regression analysis, using a *P*-value of <0.20 for the selection of variables (Royston *et al.* 2009). The prognostic accuracy of the model was estimated by the model-fit (calibration) using Hosmer–Lemeshow (H–L) test statistic and the explained variation (R^2). The discriminative ability of the model, that is, the probability to distinguish between children treated/infected once *vs.* 4–5 times, was estimated by assessing the Area Under the receiver operating characteristic Curve (AUC) (Altman *et al.* 2009).

Results

General characteristics

Of the 268 STH-positive children at baseline who participated in this study, 97.8% (262/268) were followed up at 6 months (P1), 88.8% (238/268) at 12 months (P2), 86.2% (231/268) at 18 months (P3), 87.3% (234/268) at 24 months (P4) and 78.0% (209/268) at 36 months (P5). Complete examination data from baseline until the last follow-up measurement were available for 168 children (62.7%). At baseline, 42 (25.0%) of these children were infected with *A. lumbricoides*, 82 (48.8%) with *T. trichiura* and 85 (50.6%) with hookworm. Of all children, 84 (31.3%) received one treatment, 78 (29.1%) received two treatments, 52 (19.4%) received three treatments, and 54 (20.1%) received at least four treatments.

Table 1 gives an overview of the demographic and infection characteristics for both municipalities at baseline and at each follow-up measurement. The percentage of infected children over the three-year study period is visualised in Figure 2. In general, the percentage of children infected with *A. lumbricoides* was significantly higher in SJM, while the percentage of children infected with hookworm was significantly higher in Fomento. Throughout the study period, the majority of the children

Table 1 Population demographics and characteristics of STH infections over time

				A. lumbricoides				*T. trichiura*				Hookworm				STH	
	N	Mean age (years)	Sex (% boys)	% Infected	GM epg	% Moderate-heavy infections	PRR	% Infected	GM epg	% Moderate-heavy infections	PRR	% Infected	GM epg	% Moderate-heavy infections	PRR	Cum. % infected	% Multiple infections
Baseline (P0)																	
Overall	268	8.5	61.6	29.9	1326.4	21.3	–	50.7	131.3	4.4	–	44.4	222.8	3.4	–	100.0§	22.8
SJM*	107	8.0	57.0	53.3	1554.3	26.3	–	47.7	114.6	3.9	–	25.2	124.4	0.0	–	100.0§	22.4
Fomento†	161	8.8	64.6	14.3	895.4	8.7	–	52.8	142.5	4.7	–	57.1	264.3	4.3	–	100.0§	23.0
P-value‡		0.001	0.211	<0.001	0.183	0.211		0.411	0.290	0.829		<0.001	0.004	0.270		1.000	0.353
First follow-up (6 months; P1)																	
Overall	262	9.0	62.2	8.4	2763.7	31.8	71.9	19.8	260.7	9.6	60.9	30.5	467.9	15.0	31.3	48.9	18.8
SJM*	105	8.4	57.1	18.1	3322.1	36.8	66.0	18.1	143.4	5.3	62.1	17.1	175.2	5.6	32.1	43.8	19.6
Fomento†	157	9.4	65.6	1.9	861.6	0.0	86.7	21.0	367.8	12.1	60.2	39.5	622.3	17.7	30.8	52.2	18.3
P-value‡		<0.001	0.166	<0.001	0.198	0.445		0.561	0.001	0.419		<0.001	<0.001	0.410		0.182	0.914
Second follow-up (12 months; P2)																	
Overall	238	9.5	60.9	7.6	1163.5	27.8	74.6	14.3	239.0	2.9	71.8	15.5	334.0	5.4	65.1	33.6	10.0
SJM*	82	8.7	54.9	17.1	836.5	21.4	67.9	6.1	353.3	0.0	87.2	12.2	210.2	0.0	51.6	34.1	3.6
Fomento†	156	10.0	64.1	2.6	3692.1	50.0	81.8	18.6	223.4	3.4	64.8	17.3	396.5	7.4	69.7	33.3	13.5
P-value‡		<0.001	0.166	<0.001	0.178	0.261		0.009	0.289	0.673		0.301	0.178	0.376		0.900	0.358
Third follow-up (18 months; P3)																	
Overall	231	9.9	61.9	12.1	828.8	14.3	59.5	9.5	300.8	9.1	81.3	13.9	291.8	0.0	68.7	34.2	3.8
SJM*	85	9.3	54.1	29.4	817.6	16.0	44.8	8.2	199.9	0.0	82.8	9.4	288.6	0.0	62.7	45.9	2.6
Fomento†	146	10.3	66.4	2.1	928.7	0.0	85.3	10.3	364.0	13.3	80.5	16.4	292.9	0.0	71.3	27.4	5.0
P-value‡		<0.001	0.063	<0.001	0.897	0.454		0.611	0.066	0.311		0.136	0.957	1.000		0.004	0.571
Fourth follow-up (24 months; P4)																	
Overall	234	10.4	64.5	6.0	598.8	7.1	79.9	12.0	151.4	0.0	76.3	12.8	231.4	0.0	71.2	27.8	10.8
SJM*	88	9.8	58.0	9.1	450.2	0.0	82.9	2.3	49.0	0.0	95.2	13.6	155.1	0.0	46.0	22.7	10.0
Fomento†	146	10.8	68.5	4.1	876.0	16.7	71.3	17.8	165.1	0.0	66.3	12.3	302.2	0.0	78.5	30.8	11.5
P-value‡		<0.001	0.103	0.120	0.407	0.231		<0.001	0.023	1.000		0.772	0.055	1.000		0.181	0.894
Last follow-up (36 months; P5)																	
Overall	209	11.4	64.1	7.2	646.4	13.3	75.9	6.2	114.9	0.0	87.8	18.7	247.0	7.7	57.9	29.2	9.8
SJM*	69	10.7	56.5	15.9	504.5	9.1	70.2	2.9	131.5	0.0	93.9	8.7	329.3	16.7	65.5	26.1	5.6
Fomento†	140	11.8	67.9	2.9	1278.0	25.0	79.7	7.9	112.2	0.0	85.0	23.6	234.5	6.1	58.7	30.7	11.6
P-value‡		0.001	0.108	0.001	0.407	0.423		0.163	0.834	1.000		0.009	0.537	0.353		0.489	0.468

Demographic characteristics and STH infection data are presented at baseline and five follow-up measurements for both municipalities together and separately. GM epg, geometric mean of eggs per gram in STH-positive children; PRR, Prevalence Reduction Rate; SJM, San Juan y Martínez.
*Baseline measurements in December 2003–January 2004, and study was completed in February–March 2007.
†Baseline measurements in May 2004 and study was completed in April-May 2007.
‡Chi-square test was used to assess differences between the municipalities, except for age and GM epg for which the Student's *t*-test was used.
§All children were infected with at least one STH at baseline.

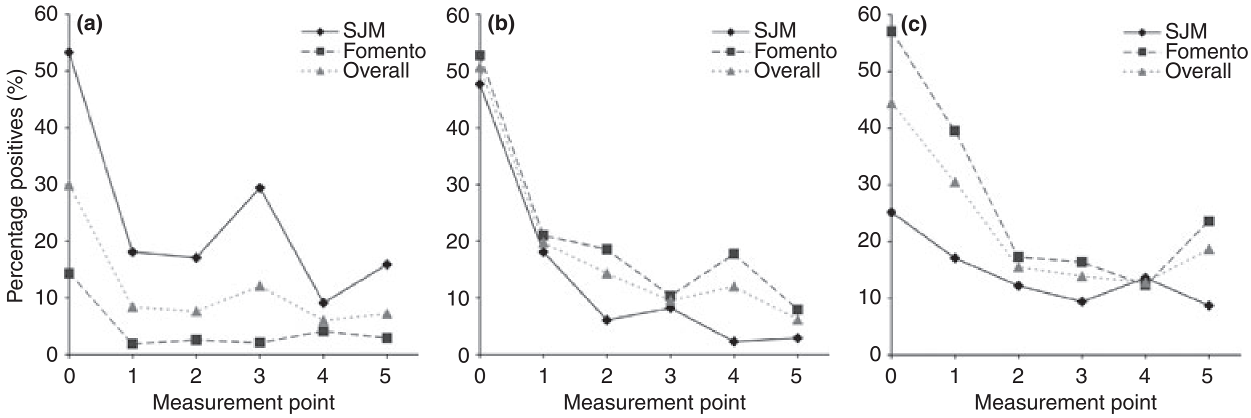

Figure 2 Percentage positives for *Ascaris lumbricoides*, *Trichuris trichiura* and hookworm infection over time. Panel (a): *A. lumbricoides* infection over time. Panel (b): *T. trichiura* infection over time. Panel (c): Hookworm infection over time.

(74.0–97.4%) was infected with only one STH, and more than half of the STH infections were of light intensity.

PRRs, CRs, CCRs and ERRs

PRRs for each measurement can be found in Table 1. Already at the first follow-up measurement, that is, after 6 months, significant PRRs were obtained for *A. lumbricoides* and *T. trichiura* ($P < 0.001$). For hookworm, this was only the case in Fomento ($P < 0.001$) and not in SJM ($P = 0.169$) where a significant PRR was obtained from the second measurement onwards, that is, after 12 months ($P < 0.001$). At the end of the study, that is, after 36 months, overall PRRs were 75.9%, 87.8% and 57.9% for *A. lumbricoides*, *T. trichiura* and hookworm, respectively ($P < 0.001$). The PRR of *A. lumbricoides* was higher in Fomento than in SJM, while the opposite was true for PRRs of *T. trichiura* and hookworm.

Table 2 shows the CRs and ERRs for each STH infection at first and last follow-up. After the first treatment (P0–P1), CRs were highest for *A. lumbricoides* (76.9%), followed by *T. trichiura* (67.4%) and hookworm (44.4%). For *A. lumbricoides*, the CR was higher in Fomento compared with SJM, while the opposite was seen for hookworm. After 36 months (P0–P5), CRs were highest for *T. trichiura* (89.7%), followed by *A. lumbricoides* (78.2%) and hookworm (70.0%). CRs only varied across municipality for hookworm.

Both at first and last follow-up, ERRs were highest for *A. lumbricoides* (98.0% and 98.7%, respectively), followed by *T. trichiura* (85.0% and 97.7%, respectively) and hookworm (63.9% and 93.6%, respectively). For

Table 2 Cure rates and egg reduction rates for each STH infection

	A. lumbricoides			*T. trichiura*			Hookworm		
	N	CR	ERR	N	CR	ERR	N	CR	ERR
Baseline to first follow-up									
Overall	78	76.9	98.0	132	67.4	85.0	117	44.4	63.9
Municipality									
SJM	56	71.4	97.3	50	72.0	89.9	26	65.4	87.2
Fomento	22	90.9	99.4	82	64.6	81.5	91	38.5	54.3
Baseline to last follow-up									
Overall	55	78.2	98.7	107	89.7	97.7	100	70.0	93.6
Municipality									
SJM	35	77.1	98.9	35	94.3	98.4	17	94.1	99.2
Fomento	20	80.0	98.4	72	87.7	97.6	83	65.1	92.2

Cure rate and egg reduction rate were calculated for each STH infection between baseline and first (6 months; 1 treatment round) and baseline and last follow-up (36 months; 5 treatment rounds), respectively. N, number of infected children for each parasite, present at both measurement points (i.e. baseline and first follow-up, or baseline and last follow-up, respectively); CR, Cure Rate; ERR, Egg Reduction Rate (in geometric mean).

A. lumbricoides and *T. trichiura*, ERRs were high and did not vary across municipality or follow-up time (all between 81.5% and 99.4%). For hookworm, ERRs at the first follow-up varied across municipality (54.3% and 87.2%) and were lower than those at the last follow-up (92.2% and 99.2%).

Figure 3 shows CCRs after 1 to 5 treatments in children with complete follow-up. CCRs differed between the municipalities for both *A. lumbricoides* and hookworm after one treatment. For *A. lumbricoides*, the CCR in SJM was significantly lower than in Fomento ($P = 0.024$), while for hookworm, the opposite was observed, although not significant ($P = 0.169$). After two treatments, differences between the municipalities disappeared and CCRs were higher than 75% for all STHs, albeit with differences between STH species (95.2% for *A. lumbricoides*, 80.5% for *T. trichiura* and 76.5% for hookworm). After three treatments, CCRs exceeded 90% with no differences between STH species (95.2% for *A. lumbricoides*, 93.9% for *T. trichiura* and 91.8% for hookworm). At the last follow-up, CCRs were 98.8% for *T. trichiura* and hookworm, and 100% for *A. lumbricoides*.

Infection risk factors

Table 3 shows that male sex, sanitary disposal (latrine or open-air defaecation) and the habit of playing in the soil were risk factors for 'persistent' infection. The H–L test statistic was not significant ($P = 0.772$), indicating that the overall fit of the prediction model was good. The model explained 9.6% of the variation in the outcome, and the AUC of the model was 0.66 (95% CI 0.56–0.75), indicating that the model performance was moderate.

Discussion

We evaluated the impact of periodic selective treatment with mebendazole on STH infections at six-month intervals for two years and a final follow-up after three years. We found that two rounds of periodic selective treatment with a single dose of 500 mg mebendazole were effective in reducing the percentage of STH infections in Cuban schoolchildren, but with important differences between helminth species.

We are aware that our study has some limitations. As for ethical reasons, STH positives could not be followed up without treatment, a comparison between treated and untreated control children could not be made. Therefore, we could not correct for any potential trends in infection regardless of treatment. Results at each measurement point were based on the parasitological examination of one stool sample per individual. In combination with low infection intensities, this may have reduced the sensitivity of the diagnostic test (Keiser *et al.* 2011) leading to an overestimation of the treatment effect. On the other hand, most other studies evaluating the efficacy or effectiveness of anthelminthics are based on one stool sample as well, allowing comparison between studies. Pre-baseline deworming or deworming outside the study protocol was not assessed and could have influenced our results. Finally, questionnaires have important inherent limitations, such as information and recall bias, which should be kept in mind when interpreting the data.

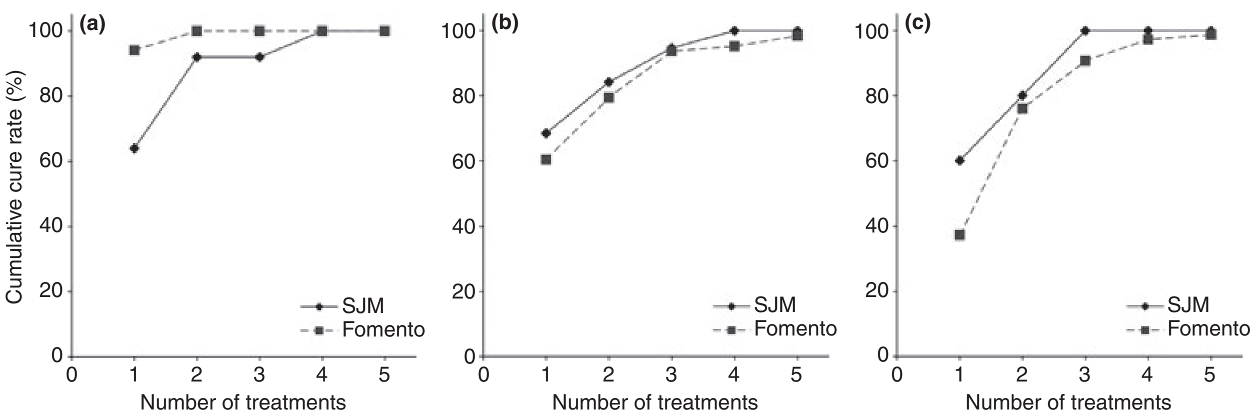

Figure 3 Cumulative cure rates for *Ascaris lumbricoides*, *Trichuris trichiura* and hookworm after number of treatments for the two municipalities. Panel (a): Cumulative cure rates for *A. lumbricoides*. Panel (b): Cumulative cure rates for *T. trichiura*. Panel (c): Cumulative cure rates for hookworm.

Table 3 Univariate associations and multivariable model of risk factors for persistent STH infections

	Univariate associations		Multivariable model	
	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value
Age (years)	1.06 (0.90–1.25)	0.477	–	
Sex (female)	0.54 (0.26–1.11)	0.091	0.58 (0.27–1.22)	0.148
Living area (urban)	0.62 (0.31–1.24)	0.175	–	
Municipality (Fomento)	1.26 (0.63–2.52)	0.512	–	
Education father (≥ grade 12)	0.60 (0.28–1.26)	0.175	–	
Education mother (≥ grade 12)	0.91 (0.45–1.85)	0.791	–	
Household income (>250 pesos/month)	1.10 (0.53–2.28)	0.806	–	
Water supply (well or river)	1.30 (0.61–2.75)	0.501	–	
Sanitary disposal (latrine or open-air defaecation)	2.64 (1.13–6.18)	0.025	2.40 (1.01–5.70)	0.048
Crowding (>2 persons/bedroom)	1.28 (0.64–2.56)	0.493	–	
Drinking unboiled water*	–	–	–	
Eating unpeeled/ unwashed fruits or unwashed vegetables	1.37 (0.65–2.89)	0.407	–	
Eating with unwashed hands	1.09 (0.55–2.18)	0.806	–	
Playing in the soil	3.51 (0.74–16.70)	0.114	2.90 (0.59–14.43)	0.192
Biting fingernails/sucking thumb	0.91 (0.45–1.84)	0.791	–	
Walking barefoot	2.56 (0.68–9.65)	0.164	–	

Risk factors for persistent STH infections were determined by comparing persistent to non-persistent infections (i.e. 4–5 infections versus one infection during the study). For the multivariable model a $P < 0.20$ was used for the selection of variables. Number of children in non-persistent infection group = 84; number of children in persistent infection group = 54.
*Too few children with positive answer ($n = 3$) for analysis.

In the following paragraphs, we compare our results with those of other, similar studies. Nevertheless, many important parameters (type of study, type of regimen, sample size, diagnostic method, number of treatments and periods after baseline) differ, which makes full comparison difficult. To aid the discussion, an overview of the most important characteristics of all related studies is provided in Table 4.

Six months after the first treatment, we found CRs of 76.9% for *A. lumbricoides*, 67.4% for *T. trichiura* and 44.4% for hookworm. A recent meta-analysis of RCTs by Keiser and Utzinger (2008) reported CRs of 95.0%, 36.0% and 15%, respectively. In the latter study, CRs were determined 10 days to four weeks after treatment. A longer follow-up period may increase the risk of reinfection, which could explain the lower CRs for *A. lumbricoides* in our study, but not the CRs for the other two species which were much higher than expected on the basis of the RCT meta-analysis. Overall, in our study, mebendazole performed better in curing STH infection than was anticipated based on the meta-analysis.

We identified only two studies that evaluated periodic selective treatment with mebendazole (see Table 4). Beltramino *et al.* (2003) evaluated, similar to our study, a single dose of 500 mg mebendazole in 55 children from a community in Argentina endemic for *A. lumbricoides* and *T. trichiura*. They presented prevalence which after 22 months and three treatment rounds had dropped by 85.8% for *T. trichiura*, while the prevalence of *A. lumbricoides* was 23.0% higher than at the start of the study. This discrepancy with our study results might be explained by the fact that they performed the study in a hyperendemic community, for which mass treatment is recommended, while our study was performed in relatively low endemicity communities, that is, target areas for selective treatment (WHO 2006). However, as the sample size is small, its conclusions are limited. Curtale (1995) evaluated two annual rounds of selective treatment by 100 mg mebendazole twice daily for three days in children from rural Nepalese villages endemic for *A. lumbricoides* and hookworm. During this regime, only the prevalence of hookworm decreased, while the prevalence of *A. lumbricoides* increased. Also this study was performed in a highly endemic region.

Four studies evaluated the effect of non-periodic selective treatment with mebendazole, that is, just one round of treatment (see Table 4) (San Sebastian & Santi 2000; Albonico *et al.* 2002; Ndenecho *et al.* 2002; Zani *et al.* 2004). In one study, a single dose of 500 mg mebendazole was evaluated in children (Albonico *et al.* 2002). As compared to our study, CRs and PRRs were higher for *A. lumbricoides* and lower for *T. trichiura* and hookworm, approaching those reported in the meta-analysis of RCTs on anthelminthic efficacy (Keiser & Utzinger 2008). The other three studies, one in adults and children (Zani *et al.* 2004) and two in children (San Sebastian &

Table 4 Overview of relevant literature about selective and mass treatment for this article

	periodic selective treatment with mebendazole		non-periodic selective treatment with mebendazole				periodic mass drug treatment with mebendazole				periodic selective treatment with albendazole
Authors	Beltramino *et al.*	Curtale	Albonico *et al.*	Zani *et al.*	Ndenecho *et al.*	San Sebastian & Santi	Beltramino *et al.*	Sinuon *et al.*	Fernando *et al.*	Albonico *et al.*	Taylor *et al.*
Country	Argentina	Nepal	Tanzania	Brazil	Cameroon	Ecuador	Argentina	Cambodia	Sri Lanka	Seychelles	South Africa
Year	2003	1995	2002	2004	2002	2000	2003	2003	2001	1996	1995
Sample size*	55	227/390/612	403	57	201	199	50	300–350/FU	349	1075/1244	153/145
Sex (% male)	NA	NA	50.1	NA	NA	NA	NA	NA	NA	NA	NA
Age range (year)	2–13	1–10	6–18	0–82	8–15	6–13	2–13	School children	6–13	3–17	4–6
Area	Urban	Rural	Urban & rural	Rural	Urban, sub–urban & rural	Rural	Urban	Rural & semi– urban	Rural	NA	Rural
Diagnostics†	KK	KK & CS	KK	KK & H–S	KK	DS	KK	KK	DS	KK	M
Type‡	SDA	SDA	SDA	SDA	SDA	SDA	MDA	MDA	MDA	MDA	SDA
Drug§	MEB	MEB	MEB	MEB	MEB	MEB	MEB	MEB	MEB	MEB	ALB
Regime¶	SD	MD	SD	MD	MD	MD	SD	SD	SD	SD	SD
# of treatments	3	2	1	1	1	1	3	4	2	3	2
Period after baseline	21 months	2 years	21–24 days	1 month	1 month	18 months	21 months	25 months	2 years	1 year	17 weeks
CRs											
A. lumbricoides	NA	NA	100.0	90.2	NA	NA	NA	NA	NA	NA	92.0**
T. trichiura	NA	NA	50.3	38.5	NA	NA	NA	NA	NA	NA	22.0**
Hookworm	NA	NA	31.3	58.5	NA	NA	NA	NA	NA	NA	89.0**
ERRs‖											
A. lumbricoides	NA	NA	97.1	NA	NA	NA	NA	NA	NA	NA	98.0**
T. trichiura	NA	NA	61.4	NA	NA	NA	NA	NA	NA	NA	37.0**
Hookworm	NA	NA	78.1	NA	NA	NA	NA	NA	NA	NA	80.0**
PRRs‖											
A. lumbricoides	[23.0]	[15.5]	93.0	NA	64.9	[15.1]	75.8	57.9	80.0	75.0	96.3
T. trichiura	85.8	NA	41.2	NA	31.3	30.8	100.0	73.7	NA	49.0	30.5
Hookworm	NA	70.1	26.1	NA	[56.3]	[62.7]	NA	66.5	57.1	33.0	93.1

CRs, Cure Rates; ERRs, Egg Reduction Rates; PRRs, Prevalence Reduction Rates; NA, not available.
*Sample size same during whole study (one number), sample size different per measurement period (numbers divided by/) or sample size per follow-up measurement (/FU).
†KK, Kato-Katz method; CS, clinical signs; H-S, Hoffman sedimentation; DS, direct smear method; M, microscopy.
‡SDA, selective drug administration; MDA, mass drug administration.
§MEB, mebendazole; ALB, albendazole.
¶SD, single dose (500 mg mebendazole or 400 mg albendazole); MD, multiple doses (100 mg mebendazole twice daily for three days).
‖Negative rates, that is, increase in prevalence and intensities, are depicted between [ ].
**Six weeks after one treatment.

Santi 2000; Ndenecho *et al.* 2002), evaluated the regime of 100 mg twice daily for three days. A multiple dose regime has been reported to be more effective than a single dose (Bennett & Guyatt 2000), but CRs and PRRs in these studies were mostly lower than those after one treatment round in our study. Moreover, all four studies were, such as Beltramino *et al.* (2003) and Curtale (1995), performed in areas with high STH prevalence where mass treatment is recommended (WHO 2006). Possibly, selective treatment may not be sufficient in highly endemic regions.

Apart from selective treatment studies, we identified four studies which evaluated periodic mass treatment with a single dose of mebendazole in children (Table 4) (Albonico *et al.* 1996; Fernando *et al.* 2001; Beltramino *et al.* 2003; Sinuon *et al.* 2003). In one study, intense health education and improvement in sanitation and safe water supply were provided in addition to anthelminthic therapy (Albonico *et al.* 1996). One study was performed in a low endemicity area (Fernando *et al.* 2001), while the others were carried out in high endemicity areas. In our study, PRRs after five treatment rounds were in the same range as those observed in these four mass treatment studies, suggesting that periodic selective treatment in low endemic areas is just as effective as periodic mass treatment in highly endemic areas.

The CCR in our study for all three STH was more than 75% after two treatments, reaching a plateau exceeding 90% after three treatments. A similar pattern was seen for the PRRs. Also other studies that evaluated bi-annual mass treatment with mebendazole (Beltramino *et al.* 2003; Sinuon *et al.* 2003) found that after one or two treatment rounds, the major reduction in prevalence was obtained, while thereafter the prevalence remained more or less stable. Hence, on average, two rounds of treatment seem necessary to substantially reduce prevalence of STH infection. Further treatment rounds maintain this level, but additional reduction or elimination is not achieved, or at least not within two to three years. More frequent treatment, for example every three or four months, may induce a stronger reduction. However, additional measures such as health education and especially sanitation remain essential to attain a sustainable reduction in transmission (Asaolu & Ofoezie 2003; Hotez *et al.* 2006).

Although ERRs are considered important for the efficacy and effectiveness of treatment (WHO 1999), most studies did not report them. Only Albonico *et al.* (2002) reported ERRs which after 21–24 days were similar for *A. lumbricoides*, lower for *T. trichiura* and somewhat higher for hookworm as compared to our six-month ERRs. According to the WHO, currently accepted thresholds for drug efficacy are an ERR of 70% in case of *A. lumbricoides* and 50% for *T. trichiura* (WHO 1999). The ERRs observed in both studies were well above these thresholds, indicating that mebendazole is effective (WHO 1999). WHO does not define thresholds for the ERR in hookworm, nor for CRs or PRRs.

CRs of mebendazole in the meta-analysis of RCTs on anthelminthic efficacy (Keiser & Utzinger 2008) were highest for *A. lumbricoides*, followed by *T. trichiura* and hookworm. In our study and the one treatment round study of Albonico *et al.* (2002), we observed a similar trend after one treatment round. However, PRRs after five treatment rounds in our study as well as in most other studies with multiple treatment rounds (see Table 4) were highest for *T. trichiura*. Furthermore, the PRRs for hookworm were better than one would expect based on the CR from the meta-analysis. A moderate and low efficacy of mebendazole for *T. trichiura* and hookworm, respectively, as reported within RCTs, does thus not necessarily correspond with moderate or low PRRs in practice within treatment programmes.

Indices of treatment impact for *A. lumbricoides* were mostly higher in Fomento than in SJM, while the opposite trend was seen for hookworm. This is likely to be related to differences in prevalence of the respective helminth species at baseline, which were lower for *A. lumbricoides* and higher for hookworm in Fomento as compared to SJM. Higher prevalence would imply faster reinfection rates and thus a lower impact of treatment.

Although albendazole has been investigated more than mebendazole, we identified only one study that evaluated periodic selective treatment (Taylor *et al.* 1995); black preschool children in South Africa were treated twice over a period of 17 weeks. The CRs observed six weeks after treatment were in the same range as those reported in the meta-analysis of RCTs on anthelminthic efficacy (Keiser & Utzinger 2008). Compared with mebendazole used in our study, albendazole performed (slightly) better for *A. lumbricoides* and hookworm and worse for *T. trichiura*, which is in accordance with the results from the meta-analysis. The choice of albendazole or mebendazole is currently mainly based on availability, policy and costs. Yet, the presence and distribution of the respective STH species may have to be taken into consideration as well. For *A. lumbricoides,* both anthelminthics are an equally good choice. Mebendazole would be the drug of choice in case *T. trichiura* is more prevalent or important than hookworm, while albendazole is preferred in the opposite case. Differences in chemosensitivity between the different species of hookworm have been observed for benzimidazoles which may have confounded the efficacy of these two drugs for this STH and warrant further investigation (Geary *et al.* 2010). Still, the development of a new anthelminthic that is equally effective against all three STHs would be preferable.

We found that male gender, sanitary disposal in latrine or open-air, and playing in the soil were important predictors for 'persistent' infection. This is not surprising as contact with soil is important in the transmission of STHs, and poor sanitation increases the chance of contamination of the soil with STH eggs and larvae (Bethony *et al.* 2006; Hotez *et al.* 2006). Also, gender differences in STH (re)infection levels have been observed before (Elkins *et al.* 1988) and are possibly related to culturally defined behavioural differences between boys and girls. However, the prediction model performed only moderate and the three risk factors explained <10% of the probability of 'remaining infected' after many treatments. This suggests that other genetic, environmental and/or host factors are of importance in the persistence of infection.

In conclusion, our results indicate that periodic selective treatment with a single dose of 500 mg mebendazole is effective in reducing the number of STH infections in low endemic settings. Although important differences were found between helminth species, two rounds of selective treatment appeared sufficient to obtain substantial reductions. The effectiveness for *T. trichiura* and hookworm was even better than anticipated based on RCT efficacy results. Risk factors for persistent infection, that is, sex, sanitary disposal and playing in the soil, should be taken into account in STH prevention and control strategies.

Acknowledgements

We thank Raúl A. Cordovi Prado for his assistance in the parasitological examinations. We also thank Meike Wördemann, Lenina Menocal Heredia and Ana María Collado Madurga for their valuable help during the study. Furthermore, we thank all children, parents, teachers, school staff, the staff in the policlinics, the health authorities and all field workers in SJM and Fomento who participated in this study. The work was financed by a grant of the Directorate-General for Development. The funder had no role in study design, data collection and analysis, decision to publish or preparation of the manuscript.

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