n. 5

*Quaderni della Società Italiana di*

# MEDICINA TROPICALE *e* SALUTE GLOBALE

## LECTURE NOTES ON TROPICAL MEDICINE AND GLOBAL HEALTH

a cura di:
Maria Grazia Bedetti, Silvio Caligaris, Federico Gobbi, Marianne Strohmeyer

Edito a cura della
Società Italiana di Medicina Tropicale e Salute Globale (SIMET)

ISBN 978-88-900025-4-0

# Integrated control of helminthiasis: example from an endemic country

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The islands of Zanzibar, Unguja and Pemba, have been historically endemic for neglected tropical diseases, and particularly for urogenital schistosomiasis (UGS), soil-transmitted helmithiasis (STH) and lymphatic filariasis (LF). Zanzibar archipelago is part of the United Republic of Tanzania and lays a few degrees south of the Equator. Tropical climate, high population density, and soil contamination with human excreta, especially in rural area, determined the very high prevalence of helminthiasis. Moreover, the presence of *Culex quinquefasciatus* was responsible for the focal transmission of *Wuchereria bancrofti*, agent of LF. In early 80's morbidity due to these parasitosis was widespread, especially in children and women of child-bearing age, and this worrying scenario led the Ministry of Health (MoH) and concerted parties to start up control efforts. This paper describes the strategies that were put in place and the efforts undertaken in the last thirty years to control and eventually to eliminate some of these parasitic infections from Zanzibar.

**Control of schistosomiasis: 1985-1990**

The Schistosomiasis Control Programme started in Pemba Island in January 1986 with support from the World Health Organization (WHO) and the Italian Cooperation. The main objectives were to reduce micro-haematuria due to *S. haematobium* by 65% and visual haematuria by 90% in two years. The secondary aim was to progressively integrate control of other communicable and parasitic diseases (as LF, STH and possibly malaria) in the control strategy [1].

The strategy was based on community-wide selective treatments in the first year, and subsequently on selective periodic treatment of schoolchildren with single dose praziquantel (PZQ) given at 40 mg/kg body weight; health education of the community (radio, poster, meetings with teachers and community leaders) complemented the drug intervention [1].

The schistosomiasis control was successful and prompted to address other helminthic infections that were public health problems in Zanzibar and that could be controlled with a similar strategy.

However, the campaigns could not be conducted smoothly, as from 1995 to 2000 there was intermittent supplies of PZQ from WHO and African Development Bank (ADB), and in 1997 29 schools in Pemba had still a prevalence of schistosomiasis > 50%. Furthermore, hemastix were relatively expensive and not easily available. In order to overcome these constraints, a questionnaire-based approach was adopted to identify children with macro-haematuria. This method was validated comparing data obtained with the questionnaire and the results of urine filtration in 10 schools. Subsequently schools were ranked according to the questionnaires and those ones with more than 50% received selective PZQ (cost 1 US$/tablet) treatment. When PZQ became cheaper (0,5 US $) and hemastix more expensive (0,3 US $), the schools with more than 50% prevalence received mass PZQ treatment according to the rank resulted from the questionnaire. The choice was driven by the cost-effectiveness of the intervention: 50% prevalence was the threshold, given those costs, as it was equal to screen everyone and treat the positive children, versus giving mass treatment without prior diagnosis to the whole school population.

**Integration with control of other helminthic infection: 1990-2000**

In late 80s' STH infections were perceived as a major public health problem in Zanzibar but there were no available data to confirm it. Between 1988 and 1991 parasitological surveys were carried out in the community and in schools to assess baseline health indicators, to better understand the geographical distribution of STH infections, to identify high risk groups, and to select the most cost-effective drug to be used in public health interventions [2].

The school survey revealed a very high prevalence of the three STH: *Ascaris lumbricoides* 79%, *Trichuris trichiura* 96 %, hookworms 94%, with 62% of the children suffering from triple infections. The epidemiological

study clarified two important elements: firstly it allowed to collect robust baseline data on prevalence, intensity, geographical distribution and age pattern of STH in Pemba island, and secondly evaluated the efficacy and safety of mebendazole 500 mg single dose to be adopted as drug of choice in the national helminth-control programme [2].
Data were also collected to assess nutritional and educational indicators. It was found out that 62% children were anaemic, (35% of iron-deficiency anaemia and 73% of severe anaemia were attributable to hookworm infections), 3,5% had severe anaemia, 45% children suffered from chronic malnutrition (stunted), and 5% children had acute malnutrition (wasted). Moreover, school attendance was studied as a mirror of childen's health; the rate was approximately 70% (140/200 school days per child), taking into account all absenteeism problems [3].
In 1992 a randomized trial was undertaken to compare single doses 500 mg mebendazole and 400 mg albendazole against the three STH [4]. The study demonstrated similar efficacy of the two drugs to control STH and also showed that a generic mebendazole was as effective as the original product and it was ten times cheaper. The reinfection rates, however, were such that after 6 months intensities of infection were similar to pre-treatment levels. These findings suggested that deworming school children every four/six months was necessary. These data were essentials to guide the national control strategy and from 1994 to 2000 all school-children were regularly treated 2-3 times a year with single dose anthelminthics (mebendazole 500 mg or albendazole 400 mg) to control morbidity due to STH infections. In addition, once a year the children were also treated with a single dose of PZQ 40 mg/Kg.
School enrollment was around 75% and means were taken to outreach the non-enrolled children. Through an intensive media campaign before the school treatment, children non-enrolled were called in by their siblings and almost 60% of those children were reached by the deworming intervention in schools.

**Monitoring and evaluation**
Any control programme needs a monitoring and evaluation plan to assess the impact of the intervention. In Pemba Island the most important indicators were selected on the basis of timeline assessment. In the short-term, the indicators were: n. children treated (coverage), n. people cured and % worm burden reduced; the n. school days attended was also calculated. In the mid-term: n. of malnutrition cases prevented, n. of severe anaemia cases prevented, and the improvement of cognitive tests in schoolchildren was also assessed. For UGS, the morbidity was measured by testing micro and macro-haematuria and by the urinary tract pathology assessed by ultrasound. In the long-term: n. bladder cancer prevented (for UGS), n. school years gained, and the DALYs gained were planned to be evaluated.
Operational research showed that schistosomiasis control goals were reached in only two years: the prevalence dropped from 55.0% to 12% and the visual haematuria was reduced by 90% in 1989.
For STH infections, after one year the cure rates were 50%, 12% and 61%, and the reductions of the worm burden were 97%, 76% and 57% for *Ascaris*, *Trichuris* and hookworm infection, respectively [5]. Regarding nutritional indicators, deworming intervention reduced severe anaemia by 39%, significantly improved iron stores and growth of children (20% in weight and 7% in height). Iron and mebendazole had also a positive effect on motor and language development of pre-school children and periodic mebendazole treatment reduced wasting malnutrition in children. The blood loss prevented only by deworming 3 times/year was estimated to be about 250 ml, a quite significant amount. The school attendance was improved by 14% [3].
In 2000 the impact of periodic deworming on schistosomiasis was evaluated in an endemic village: visual haematuria dropped from 15% (1988) to 1.5%, severe infections (> 50 eggs/10 ml of urine) dropped from 18% (1988) to 8%, severe urinary pathology in adult males monitored by ultrasound was reduced from 40% (1988) to 19% [6].
The cost of deworming campaigns was also calculated, including cost of drugs, their distribution and the monitoring survey, and summed up to $ 0.19 as yearly cost for a child treated with benzimidazoles three times/year. The cost per case of severe anemia averted was 15 US $ and only 0,01 US $ was the cost for any school-day gained/child.

**Programme for the elimination of LF**
Since the 70's LF was abundant in Zanzibar with focal transmission, and elephantiasis cases were visible and scattered both in Pemba and Unguja islands. Endemic foci were identified by previous surveys showing prevalence between 20% and up to 50% in Unguja, and between 10% to15% in Pemba island.
Following the WHO recommendation to undertake LF elimination in any area with more than 1% prevalence, in 2001 Zanzibar started the Global Programme for Elimination of Lymphatic Filariasis (GPELF). The strategy was based on at least 6 yearly rounds of Mass Drug Administration (MDA) with ivermectin (6 mcg/kg) and albendazole 400 mg to the whole community, except pregnant and lactating women and children below 5 years of age. The other pillar of the GPELF was the management of LF morbidity, mitigating lymphedema and treating sick people with health practices to relief their morbidity burden. Hydrocele surgery camps were also successfully set up. The GPELF needed almost a military approach with a National Task Force that coordinated

an array of partners (pharmaceutical companies, International Agencies, WHO, local reference laboratories, local leaders, universities, and civil society). Ahead of the drug distribution an intense information and sensitization campaign was carried out in order to foster social mobilization to maximize coverage of MDA. Filaria prevention agents (FPA) were hired to distribute the drugs countrywide in 2 days. Adverse events were monitored, reported and appropriately managed [7]. The last MDA involved the administration of triple therapy with albendazole, ivermectin and praziquantel, and for the first time triple therapy was implemented in community campaigns and proved to be feasible and safe.
This strategy was successfully implemented with good drug coverage (average of >80% in 5 years) and led the prevalence of microfilariaemia to drop to <1% in sentinel sites, a threshold for considering discontinuation of MDA campaigns for LF. Morbidity was also reduced by almost halving lymphedema and hydrocele patients. In addition, as side benefits of ivermectin treatment, there was a 60-98 % decline in scabies infections. Another subsequent study revealed that also infection by another neglected helminth, *Strongyloides stercoralis,* have been drastically reduced in Zanzibar due to the periodic use of ivermectin.
However, before declaring Zanzibar free from LF, a transmission assessment survey (TAS) after 6 years of MDA was carried out in 2012. School children in all four districts, aged between 6-8 years who were treatment-naive were randomly selected for participation. Data showed that the prevalence of filaria antigen among this population was >1% for some sites in Unguja and >5% for some sites in Pemba. These results indicated that LF transmission had not halted and that MDA with ivermectin should have been re-introduced.

**Elimination of UGS**
In 2010 the MoH Zanzibar revised the strategy for control of STH and schistosomiasis, recommending increasing the frequency of PZQ delivery (from single annual to biannual). Furthermore, Zanzibar was selected by SCORE (Schistosomiasis Consortium for Operational Research and Evaluation) for trialing additional interventions, molluscicide and behavioural change, for progressing towards elimination of schistosomiasis. An alliance was formed in 2012 including various partners (WHO Geneva, WHO AFRO, Schistosomiasis Control Initiative, Swiss Tropical and Public Health Institute, Natural History Museum - London, and Zanzibar Ministries) and was called the Zanzibar Elimination of Schistosomiasis Transmission (ZEST). The aim of ZEST was to assess the impact of three parallel control interventions in Pemba:- (i) The National Control Programme (NCP) alone based on PZQ treatment and health education, ii) NCP plus molluscicide and iii) NCP plus behavioural modification. Fifteen Shehias (smallest administrative units) out of a total of 45 were randomized to each arm [8].
In addition, the National Institute of Parasitic Diseases, China, was interested to try out the model they have used to control/eliminate Asian schistosomes and to apply their expertise in the sub-saharan Africa setting. Zanzibar was selected among the pilot countries and substantial resources were allocated.
The SCORE project is just finished and its outcome is being analyzed. However, ad interim analysis showed that prevalence dropped from 8% in Unguja and 15% in Pemba in 2011 to 3% in Unguja and 5% in Pemba in 2014, but with some persistent hotspots in which transmission was not halted.

**Challenges and perspectives**
From 2000 to 2006 Zanzibar was a perfect example of integrated control of helminthiasis. School children were treated every year with praziquantel plus albendazole or mebedazole and after 6 months ivermectin plus albendazole was delivered to the whole community. Health education on basic hygienic practices and on use and maintenance of latrines was given before any deworming campaign. Latrines were built in schools by UNICEF, and safe water supplies were developed both in schools and in villages with support from UNDP and ADB. PZQ and benzimidazoles were available in peripheral health centres.
However, despite almost three decades of control efforts, prevalence of STH is nowadays still high, and UGS and LF are yet to be eliminated.
Several challenges have to be identified and addressed.
-) After many years of treatment, community fatigue was perceived and the compliance of MDA has to be sustained.
-) A solid surveillance system for LF and eventually UGS should be built. Efforts must be focused on the identified hot spots of schistosomiasis transmission, and intensively foster integrated control (WASH, vector control) for the elimination of transmission.
-) Drug efficacy of benzimidazoles and PZQ must be monitored in the area with high dug pressure, and combination of anthelminthics, especially against the persistent worm *T. trichiura,* should be tested.
-) Finally, helminth control must be kept sustainable through better integration. Teachers and drug distributors demand incentives and MDA activities are not cheap. Although deworming medicines are so far available through donation from drug companies, their cost of distribution and monitoring should be sustained by local MoH and communities, without depending on external support.
A concerted effort should be made by the MoH and partners for a final push to eliminate helmithiasis as public health problems in Zanzibar.

**Figure 1 - Summary of helminth control in Pemba**

| | 1986-1988 | 1989 -1993 | 1994-1998 | 1999-2002 | 2003 | 2004 | 2005 | 2006 | 2007 | 2008 | 2009-2011 | | 2012-2013 | 2014-2017 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Praziquantel (PZQ) | 1 | 2 | 3 | 4 | | 6 | | 7 | | | 9 | 10 | 11 | |
| Mebendazole (MBZ) | | | 3 | | | | | 8 | | | | | | |
| ALB + Ivermectin (IVM) | | | | | 5 | | | 7 | | | | | | 12 |
| Albendazole (ALB) | | | | | | 6 | | | | | 9 | | 10 | 11 |

| | | |
|---|---|---|
| | 1 | Selective chemotherapy to children and adults - test and treat campaign, twice a year |
| | 2 | School targeted treatment, twice a year |
| | 3 | Zanzibar Helminth Control Programme (ZHCP) initiated<br>PZQ for school targeted treatment, only in high prevalence schools<br>MBZ for school targeted treatment, twice a year |
| | 4 | Irregular distribution □school selective or targeted treatment depending on prevalence, according to the rank |
| | 5 | GPELF: Community MDA (> 5 years of age), once a year. In 2006 PZQ was also included in the package and the three drugs were delivered together in the communities in MDA (7). |
| | 6 | ZHCP ,> 5 years of age, once a year<br>2004 - 2005, Community MDA in Pemba (supported by SCI - Schistosomiasis Control Initiative)<br>2006, School based treatment in both Islands |
| | 7 | Integrated Triple Drug Administration (ALB+IVM+PZQ), Community MDA, only once |
| | 8 | Preschool targeted treatment (12 - 59 months), twice a year, supported by UNICEF |
| | 9 | School targeted treatment, once a year: (The treatment was partially implemented), no PZQ distributed |
| | 10 | School targeted treatment, once a year |
| | 11 | School targeted treatment followed by MDA twice /year |
| | 12 | ALB+IVM reintroduced after the TAS |

**REFERENCES**


1. Savioli L, Dixon H, Kisumku UM, Mott KE. Control of morbidity due to *S.haematobium* on Pemba Island: programme organization and managment. Tropical Medicine and Parasitology 1989, 40, 189-194.
2. Renganathan E, Ercole E, Albonico M, De Gregorio G, Alawi KS, Kisumku UM, Savioli L. Evolution of operational research and development of a national control strategy against intestinal helminths in Pemba Island, 1988-92. Bulletin of the World Health Organization 1995, 73(2), 183-190.
3. Stoltzfus RJ, Albonico M, Chwaya HM, Tielsch JM, Schulze KJ, Savioli L. Effects of the Zanzibar school-based deworming program on iron status of children. American Journal of Clinical Nutrition. 1998, 68(1), 179-186.
4. Albonico M, Smith PG, Hall A, Chwaya HM, Alawi KS, Savioli L. A randomised controlled trial comparing mebendazole and albendazole against Ascaris, Trichuris and hookworm infections. Transactions of the Royal Society of Tropical Medicine 1994b, 88(5), 585-589.
5. Albonico M, Stoltzfus RJ, Savioli L, Chwaya HM, d'Harcourt E, Tielsch J. A controlled evaluation of two school-based antihelmintic chemotherapy regimens on intensity of helminth infections. International Journal of Epidemiology 1999, 28(3), 591-596.
6. Hatz C, Savioli L, Mayombana C, Dhunputh J, Kisumku UM, Tanner M. Measurement of schistosomiasis-related morbidity at community level in areas of different endemicity. Bulletin of the World Health Organization 1990, 68, 777-787.
7. Mohammed KA, Molyneux DH, Albonico M, Rio F. Progress towards eliminating lymphatic filariasis in Zanzibar: a model programme. Trends in Parasitology 2006, 22(7), 340-4.
8. Knopp S, Mohammed KA, Ali SM, Khamis IS, Ame SM, Albonico M, Gouvras A, Fenwick A, Savioli L, Colley DG, Utzinger J, Person B, Rollinson D. Study and implementation of urogenital schistosomiasis elimination in Zanzibar (Unguja and Pemba islands) using an integrated multidisciplinary approach. BMC Public Health 2012, 30; 12 (930).