**Institution: The University of Edinburgh**

**Unit of Assessment: UoA5: Biological Sciences**

**Title of case study:**
**03. Pre-school children are now included in schistosomiasis prevention programmes.**

## 1. Summary of the impact

**Impact on health and public policy:** The World Health Organisation (WHO) now recommends that children under 6 years, who had hitherto been excluded from drug treatment, should be included in schistosome control programmes, following research by UoE that reversed previous assumptions about schistosomiasis infection rates in pre-school children (1-5 year olds) and demonstrated the safety and efficacy of Praziquantel (PZQ) treatment in this age group.

**Beneficiaries:** WHO policy change affects children under the age of 6 years in countries affected by schistosomiasis (up to 10 million children). 350,000 pre-school children in Zimbabwe have so far been treated with PZQ, with a further 1.2 million already identified by the Ministry of Health for inclusion in the next round of MDA to start in October 2013

**Significance and Reach:** 5-10 million pre-school children in Africa (WHO estimates) now merit treatment. Urogenital schistosomiasis affects more than 100 million people in Africa; in affected populations, children carry the heaviest burden of the disease. Following the recommendations from the WHO on preschool children, 4 countries (Niger, Malawi, Uganda and Zimbabwe) have so far included pre-school children in their schistosome control policies with Zimbabwe currently implementing this.

**Attribution**: Dr Francisca Mutapi led the research at UoE establishing the evidence base for the safety and efficacy of PZQ. The study was collaborative with UoE leading the research and conducting the laboratory studies, while collaborators at the University of Zimbabwe and National Institutes of Health Research in Zimbabwe organised the fieldwork.

## 2. Underpinning research

Urogenital schistosomiasis (bilharzia) is a chronic disease caused by the parasitic worm *Schistosoma haematobium.* Research led by Francisca Mutapi at UoE has focused on determining host and parasite factors that influence patterns of infection and disease in human populations to inform vaccine development and optimization of drug intervention strategies. This research has focused on the infection process and factors influencing the development of schistosome-specific protective acquired immunity and drug effects on the parasite and host. This research showed that the drug praziquantel (PZQ) - the only control measure currently available - accelerates the development of acquired schistosome-specific immunity [1, 2], favouring responses associated with protection against re-infection with the parasites. Subsequent research on parasite-induced host immune responses includes the 2012 PNAS paper [3] which answered a long-standing question showing that protective infection to *S. haematobium* is primarily an anti-fecundity response stimulated by the death of adult worms. Most recently, a vaccination strategy for not only schistosomiasis but other parasitic diseases such as malaria has been proposed in a review paper (Mutapi, F., et al. (2013) Infection and treatment immunizations for successful parasite vaccines. *Trends Parasitol* 29, 135-141).

Prior to 2007 it was thought that PZQ would not be efficacious in young children aged 1-5 years due to the assumed lack of schistosome-specific immune responses to synergise with the drug. Furthermore, it was widely believed that pre-school children were not frequently exposed to infective water to acquire clinically significant levels of infections. In 2006/07 Dr Mutapi designed and co-supervised a study that demonstrated the need and beneficial effect of PZQ treatment of primary school children [4]. Subsequently, WHO funded a full safety and efficacy study for the administration of PZQ, to pre-school age children in four African countries including a study in Zimbabwe led by UoE [5]. The Zimbabwe study compared the need, efficacy and side effects of PZQ in 1-4 year old preschool children vs. 6-10 year old primary school children (the WHO-recommended target population for helminth control programmes). The study showed that (i) infection levels in preschool children were higher than in adults already included in control

programmes, (ii) PZQ was safe in this age group, with fewer side effects that in primary school children, and (iii) PZQ was efficacious in this age group, with infection reduction rates comparable to those in primary school children.

Key personnel: Dr Francisca Mutapi (UoE lecturer, 2002-present) was the Principal Investigator throughout and directed the safety and efficacy study. Nausch (2008-present), PDRA in Mutapi's group and PhD student Rujeni carried out the fieldwork from 2008 to 2010. Mutapi was the associate supervisor of then-PhD student Midzi alongside Mduluza (University of Zimbabwe); she subsequently designed and analysed the Prevalence Survey with Midi (University of Zimbabwe). Maizels [1,2], Savills [3] and Woolhouse [3] (all UoE) collaborated on the underlying research together with UoE PhD student Mitchell [3] and with Turner and Burchmore of Glasgow University [1,2].

## 3. References to the research


1. Mutapi, F., Burchmore, R., Mduluza, T., Foucher, A., Harcus, Y., Nicoll, G., Turner, C.M., and Maizels, R. (2005) Praziquantel treatment of individuals exposed to *Schistosoma haematobium* enhances serological recognition of defined parasite antigens. *J Infect Dis* 192, 1108-1118 doi: 10.1086/432553 **41 Scopus citations at 16/10/2013**

2. Mutapi, F., Burchmore, R., Mduluza, T., Midzi, N., Turner, C.M., and Maizels, R. (2008) Age-related and infection intensity-related shifts in antibody recognition of defined protein antigens in a schistosome-exposed population. *J Infect Dis* 198, 167-175 doi:10.1086/589511 **16 Scopus citations at 16/10/2013**

3. Mitchell, K.M., Mutapi, F., Savill, N.J. and Woolhouse, M.E.J. (2012). Protective immunity to *Schistosoma haematobium* infection is primarily an anti-fecundity response stimulated by the death of adult worms. *Proc. Nat. Acad. Sci. USA*, **109**, 13347-13352. doi: 10.1073/pnas.1121051109. **2 Scopus citations at 16/10/2013**

4. Midzi N, Sangweme D, Zinyowera S, Mapingure MP, Brouwer KC, Kumar N, Mutapi F, Woelk G. and Mduluza T. Efficacy and side effects of praziquantel treatment against Schistosoma haematobium infection among primary school children in Zimbabwe. (2008). *Trans. R. Soc. Trop. Med. Hyg*. **102**, 759-66. doi:10.1016/j.trstmh.2008.03.010 **15 Scopus citations at 16/10/2013**

5. Mutapi, F., Rujeni, N., Bourke, C. Mitchell, K., Appleby, L., Nausch, N., Midzi, N. and Mduluza, T. (2011). Schistosoma haematobium treatment in 1-5 year old children: safety and efficacy of the antihelminthic drug praziquantel. *PLoS Negl. Trop. Dis*. **5** e1143. doi**:** 10.1371/journal.pntd.0001143. **19 Scopus citations at 16/10/2013**


Peer reviewed grant funding won:

Immuno-epidemiology of schistosomiasis: from the mouse model to natural human infection. Period: 1/10/07 - 28/02/11. Funding organisation: UK-based charities. Total award: £303,390, Principal investigator: Francisca Mutapi

Health benefits of repeated treatment in paediatric schistosomiasis. Period: 1/04/11 - 31/03/14. Funding organisation: Non-EU-based charities. Total award: £199,528, Principal investigator: Francisca Mutapi

Monitoring the effects of mass drug administration of praziquantel' in Zimbabwe's National Schistosome Control programme. Period 1/10/12 -30/1/14 Funding Organisation: Schistosome Control Initiative (SCI).Total Award (£100,000) Principal Investigator: Francisca Mutapi

## 4. Details of the impact

Larval forms of the schistosomiasis parasite are released from freshwater snails and penetrate the skin when an individual comes into contact with infective water. Schistosomiasis is the second

(after malaria) most important parasitic infection of public health concern in Africa, with children being most at risk of infection and disease; urogenital schistosomiasis affects more than 100 million people in Africa. Symptoms of this neglected tropical disease are caused not by the worms themselves but rather the host's immune response to the worm's eggs. In affected populations, children carry the heaviest burden of the disease with schistosomiasis causing haematuria, nutritional deficiencies, anaemia and growth retardation amongst other health issues. Untreated infections acquired in childhood can lead to kidney and bladder pathology, bladder cancer, reduced fertility and susceptibility to HIV infection.

Control of schistosomiasis is based on preventive treatment, snail control, improved sanitation and health education. Morbidity due to schistosomiasis is currently controlled by the periodic, targeted treatment of infected people with the anti-helminthic drug, PZQ. Children aged under 5 had been excluded from schistosome control programmes for several reasons: a lack of safety data on PZQ in this age group, misconceptions about the level of infection in pre-schoolers and also previously-held thoughts that the immune system in the under 5s was not sufficiently developed to act synergistically with PZQ. UoE research demonstrated how PZQ treatment influences acquired immunity [1,2,3] and showed that PZQ is effective and well-tolerated by pre-school children [5], and that the effects of PZQ on the immune responses to schistome antigens and allergens in the under 5s were similar to those observed in older children [2,4,5]. This research, together with that of two other groups funded by WHO to investigate the use of PZQ in this age group in Mali and Sudan, was presented at a WHO workshop in September 2010. As a result of these findings, the main recommendation of this meeting was the inclusion of pre-school children aged 5 years and under in schistosome control programmes [a, b].

Until a paediatric formulation of PZQ is in use, PZQ doses to children are calculated based on patient weight. However, in the field, correct dosages of PZQ need to be administered quickly to large groups of children with minimal equipment for the task. Therefore, in the field a PZQ 'dose pole' measuring height is used as a proxy for weighing scales for calculating the dose of PZQ. The WHO meeting recommended that the PZQ dose pole be evaluated for extended use in pre-school children. Data from several African countries including that supplied by the UoE research [4, 5] was used to validate the use of the PZQ pole in children aged 5 and under [c], and it is now deployed in the field. [f].

Following WHO recommendations, which require a national survey and plan of action before implementation of a national helminth control programme, Mutapi collaborated with the University of Zimbabwe and Ministry of Health to conduct a National Schistosomiasis Survey throughout Zimbabwe, formulate a national Neglected Tropical Diseases Control Policy and draft a plan of action. This National Prevalence Survey was carried out in 2010 to ascertain levels of schistosome infection across the country. This allowed stratification of the control programme according to schistosome infection levels and formulation of a treatment strategy using WHO treatment guidelines. Mutapi was involved in the design of the national survey protocol and subsequent data analysis, drawing on findings from the previous UoE research. The report from this survey resulted in a proposal to the Ministry of Health in Zimbabwe for a national control programme and the formulation of a plan of action for schistosome control. The resulting policy was published in July 2011 as a National Control Policy of Zimbabwe [d, f]. This policy included treatment of pre-school children as a result of the UoE/UoZ research [5], making Zimbabwe's MDA programme the first control programme worldwide that includes the treatment of children under the age of 5 years. As a result of the WHO policy change and the Zimbabwean Control Programme, 2 million pre-school children in Zimbabwe are now included in a national control programme. In September 2012 a mass drug administration (MDA), including pre-school children for the first time ever, was delivered through the country's network of schools and health facilities in all districts of Zimbabwe with support from WHO, UNICEF, WFC and other development partners. 346,970 pre-school children received treatment against Schistosomiasis for the first time [e, f].

UoE is leading a monitoring and evaluation survey of the Zimbabwean control programme and we have shown that the first MDA has been extremely successful in reducing *S. haematobium* infection amongst pre-school children. This new treatment strategy arising from the UoE research is therefore also instrumental in reducing the risk for pre-school children of developing irreversible

complications in adulthood.

The Chair of the 2010 WHO workshop on schistosomiasis states:

> *"Internationally, this on-going programme and evaluation study in Zimbabwe has many ramifications. Niger, Uganda and Malawi are now expanding the delivery of treatment to pre-school age children. By this token the work is of international importance. It will help tens of thousands of children in the short term and several million in the long term."* [g]

## 5. Sources to corroborate the impact

The Tiny URL provide a link to archived web content, which should be accessed if the original web content is no longer available

a. Report of a meeting to review the results of studies on the treatment of schistosomiasis in pre-school-age children. World Health Organisation 2011. ISBN 978 92 4 150188 0 http://whqlibdoc.who.int/publications/2011/9789241501880_eng.pdf

   See pp.10-12 for reference to Mutapi's work. [pdf of copy available on request]

b. Preventive Chemotherapy and Transmission Control Unit, Control of Neglected Tropical Diseases, World Health Organization. Corroboration that UoE research was key to the working group that concluded that PZQ treatment was safe, efficacious and necessary for Pre-school children.

c. Information on extended dose pole validation is presented in Stothard, J.R., et al. (2011) Closing the praziquantel treatment gap: new steps in epidemiological monitoring and control of schistosomiasis in African infants and preschool-aged children. *Parasitology* 138, 1593-1606. Zimbabwe study data in Table 1 and Figure 2. [copy available on request]

d. "National policy for the control of soil transmitted helminths, schistosomiasis and other neglected tropical diseases in Zimbabwe". July 2011. [PDF available on request]

e. WHO news documenting the launch of the Zimbabwean MDA: http://www.afro.who.int/en/zimbabwe/press-materials/item/4937-zimbabwe-launches-mass-drug-administration-against-schistosomiasis-and-intestinal-worms.html

   or http://tinyurl.com/lj7m72m

f. Director Epidemiology & Disease Control, Ministry of Health & Child Welfare, Zimbabwe. Can provide corroboration to confirm use of PZQ extended pole in the field, the Zimbabwe National Control programme and MDA. Report on the successful completion of the 1st wave of the MDA in Zimbabwe available on request.

g. The Chair of the 2010 WHO workshop can provide corroboration of the influence of UoE research on WHO policy.