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Schistosomiasis in African infants and preschool children: to treat or not to treat?

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The occurrence of schistosomiasis in African infants and preschool children has been largely overlooked, with preventive chemotherapy usually focused on school-aged children instead. Two recent surveys by Bosompem et al. and Odogwu et al. have shown that schistosomiasis in younger children is much more common than previously thought. This article highlights the importance of the disease in this age group and discusses the future prospects for schistosomiasis control.

Control of schistosomiasis

International interest and political commitment for control of helminthic diseases in sub-Saharan Africa has grown substantially in recent years with schistosomiasis on the international health agenda. Of central importance to control of helminthic diseases is large-scale interventions that administer safe, efficacious and low-cost medications to target groups. For modest financial outlays, preventive chemotherapy-based programmes can deliver public health gains [1] but one of the future challenges on the ground lies with identification of the best drug strategies and delivery systems. This is necessary to dovetail appropriate anthelmintic drug regimes to co-endemic areas and those sections of the local populace in which infections overdispersion of schistosomiasis, preventive chemotherapy usually represents locations where healthcare facilities are meagre, so disease surveillance has been largely ignored from a control perspective.

The treatment pattern of schistosomiasis is in contrast to other helminth infections. For example, soil-transmitted helminthiasis (STH) can be common in preschool children [3] and this age group also contributes to transmission of lymphatic filariasis [4]. As a result, administration of albendazole (ALB) or mebendazole to children older than one year is recommended by the World Health Organization (WHO: http://www.who.int) for the control of STH [2]. For lymphatic filariasis, any child aged two years and over is considered eligible for mass drug administration (MDA) with diethylcarbamazine and ALB [2]. Use of ivermectin (IVM), in combination with ALB, is restricted to children ≥15 kg or ≥90 cm in height [2]. In countries where IVM and ALB are administered, Gyapong has shown that a large proportion of preschool children is, in fact, targeted during MDA because the threshold height of the treatment pole (90 cm) often selects children five years old and younger [5].

Schistosomiasis and the younger child

Contrary to commonly held assumptions, schistosomiasis can occur in infants and preschool children. As Jordan and Webbe put it 'if transmission is occurring in the 'back yard', some children will be infected in the first year or two of life but more usually they probably acquire their first exposure when they accompany another member of the family to an infested river or pond' [6]. Historically, several reports have demonstrated the occurrence of schistosomiasis, either urinary or intestinal, in infants and preschoolers [7–13].

Two recent studies have better quantified the prevalence and intensity of infections in younger children and clearly show that schistosomiasis, either urinary (caused by Schistosoma haematobium) or intestinal (caused by Schistosoma mansoni), can be common [14,15]. Because directed field surveys were used, this new evidence is particularly important for two reasons: (i) high schistosomiasis-transmission environments usually represent locations where healthcare facilities are meagre, so disease surveillance has been largely ineffective and failed to target this age group; and (ii) even if

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such healthcare facilities were locally accessed, routine parasitological screening misses many infected cases because light infections predominate [16] and parasite detection thresholds, at least in non-human primates, have been shown to be poor [17].

**Directed field surveys**

In Ghana, egg-patent infections (where a schistosome ovum could be seen) with *S. haematobium* were found in infants of four months and over, which results in a general parasitological prevalence of 11.2% [14]. Using a monoclonal antibody dipstick, infection prevalence was found to be about threefold higher (i.e. ~35%) because children probably harboured infections that were prepatent (where immature worm pairs were yet to commence egg deposition) or that were below the sensitivity threshold of conventional parasitological diagnosis. Furthermore, those infections encountered in infants who were not visiting water-contact sites were indicative that their domestic water transported home for household use was infested with cercariae.

In Uganda, nearly 50% of children under three years of age living along the northern shoreline of Lake Victoria had *S. mansoni* infections [15]. Egg-patent infections were found in children aged one year and above but younger children (e.g. a five month old boy) were also likely to be infected as evidenced by the presence of schistosome circulating cathodic antigens in their urine. Water-contact questionnaire studies showed that the child’s history of exposure was contingent upon the bathing practices of its own mother and/or older relatives. Infected children were more likely to have infected mothers because both mother and child frequented the same site or shared domestic water. These children were unknowingly exposed by their guardians’ daily washing and bathing of them, either at home or on the immediate lakeshore with water directly drawn from the lake (Box 1) [15].

**Consequences of early infection**

Although intensities of infection were usually light, the immediate consequences of infection are difficult to assess because the proportionality between intensity and...
morbidity seen in older children (aged 6–15 years) might be inapplicable in this younger age group (aged 0–5 years). For example, the clinical importance of STH in younger children is being re-evaluated in terms of cryptic (or subtle) morbidity [15]. This might also occur with schistosomiasis because cryptic morbidity associated with this disease is leading to debate [18]. Without further evidence, however, it is difficult to speculate how the immune system of the infected younger child is primed for immediate or later life-evolved morbidity as mediated by subsequent detrimental immune responses. For example, presentation of certain antigens in early life might lead to either immunotolerance or immunopathology. With regards to immunopathology, there is a surprising number of school-aged children with advanced hepatosplenic schistosomiasis in these Ugandan lakeshore villages [19]. This indicates that early exposure predisposes to heightened future morbidity or, at least, that such cases arose from a much longer duration of infection. Future longitudinal studies profiling biomarkers of disease in this age group are needed and should also assess any interplay with other diseases (e.g. malaria and HIV) before and after PZQ treatment.

**Administration of PZQ in younger children**

From an ethical perspective, infections in children of any age should be treated but, in contrast to other anthelmintic drugs, three major constraints exist in the use of PZQ in infants and preschool children. First, there is insufficient information documenting the safety of PZQ in children under four years of age [20] and this could prevent its inclusion in large-scale interventions that distribute drugs without direct medical supervision. This might be overly conservative because in confirmation of the excellent safety and tolerability of PZQ, Bosompem et al. and Odogwu et al. witnessed no immediate adverse reactions [14,15]. Second, conventional tablets are normally rejected by younger children because of their size and taste. Although syrup formulations exist for PZQ in some countries, these are not widely available and are expensive compared to tablets. Many sub-Saharan countries are yet to register these products with their appropriate drug administration agencies, so importation of medications remains unclear. As a stop-gap, it is possible to break PZQ tablets into smaller pieces or to crush them in flavoured syrup, which would make treatment both palatable and acceptable. This is particularly important to mitigate any risks associated with choking upon large tablets. Because this is time consuming, the speed and ease of administration of treatment is much slower and might, therefore, be impractical during large-scale interventions. Third, a height pole used to determine the tablet dose for children <94 cm high is yet to be developed, so it is necessary to weigh children to calculate the appropriate dose of PZQ (40 mg kg⁻¹). Because this requires the use of measuring scales, it is also likely to impose a logistic bottleneck.

**To treat or not to treat?**

Should administration of PZQ to infants and preschool children be recommended in the future? In places where local transmission of schistosomiasis is intense, it is certain that younger children will be at risk of infection, especially if their bathing and drinking water is drawn directly from schistosome-infested sources. In these environments, the classical model that sees infection in school-age childhood as a risk factor for developing overt morbidity in adulthood might be translated into one that sees infection in preschool-age childhood as a risk factor for developing overt morbidity in school-age childhood. In this regard, the first practical recommendation would be to include preschool children of four years of age and older and >94 cm high among the target groups in those areas in which large-scale preventive chemotherapy interventions against schistosomiasis are carried out.

For children aged under four, inclusion seems impractical because of the above constraints. Therefore, in high-risk communities where local prevalence of schistosomiasis is known to be substantive (i.e. prevalence among school-age children >50% [2,12]), a solution would be to include PZQ treatment in the routine maternal and child-health interventions. These target infants and preschool children at the primary health care clinic level and include childhood immunizations and micronutrient supplementation. Because scales are usually available, breaking or crushing an appropriate amount of PZQ tablet(s) in flavoured syrup should be feasible for treatment. Monitoring, managing and recording any immediate adverse post-treatment reactions should also be possible. In this individual case-management setting, it is up to the informed health worker and supporting health team to balance the risks of treating versus not treating by taking into account the local water hygiene and sanitation factors and the immediate disease burden. In this manner, we firmly believe that the benefits of PZQ treatment would exceed any associated risks enabling infants and preschool children to benefit from better health without an insidious burden of schistosomiasis.

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**References**


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The different functions of skin dendritic cell subsets during *Leishmania* infection were recently reviewed by Ritter and Osterloh. In their article, they propose a new role for epidermal Langerhans cells and dermal dendritic cells to explain the events that take place after inoculation by *Leishmania*.

**The many functions of dendritic cells**

Dendritic cells (DCs) are a heterogeneous and widely distributed group of migratory bone marrow-derived cells that specialize in the recognition, uptake, transport, and processing of pathogen antigens. DCs have a key role in the adaptive immune response because they are the only antigen-presenting cell able to prime naïve T lymphocytes. DCs are also known to activate natural killer cells [1] and are involved in the induction of tolerance to self-antigens in peripheral CD4+ and CD8+ T cells [2]. The expression of multiple cell-surface markers has also enabled the correlation between DC-specific subtypes and distinct effector functions [3].

Langerhans cells (LCs) are a specific subset of skin DCs that form a dense network in the supra-basal layer of the epidermis. LCs are thought to serve as sentinel cells that survey the epidermis and are also speculated to have protective functions. It was widely accepted that upon microbial infection, LCs take up antigens from the pathogen and then migrate to a T-cell-dependent area of the skin-draining lymph nodes in order to prime naïve T cells, a life cycle that established a paradigm for the other DCs [4] (Box 1). However, recent studies of the multiple DC types found in the lymphoid organs of mice and humans have shown that most DC subsets fail to follow the life cycle typified by LCs. This has given rise to a scientific debate on the functions of LCs in vivo [5]. A recent article by Ritter and Osterloh that revises the role of DC subsets in the experimental model of leishmaniasis has added to the discussion [6]. The authors propose that the T-cell immune response against *Leishmania major* is, in fact, generated by dermal DCs and that LCs have a regulatory function instead and might be responsible for the suppression of the inflammatory response against *L. major* infection.

**Visualizing skin dendritic cells**

Ritter and Osterloh [6] reconsider the new findings on the biological role of both LCs and dermal DCs during *L. major* infection. These data enable a more accurate view of the events that currently take place during parasite infection. Previous studies on the experimental mouse model of leishmaniasis led to the ‘LC paradigm’ for this parasitic infection. The cutaneous localization of LCs, the ability of these cells to phagocytose *Leishmania* parasites and to stimulate *L. major*-specific T-cell proliferation and lymphokine production *in vitro*, led Moll to propose that