FEMALE GENITAL SCHISTOSOMIASIS Q&A

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Schistosomiasis is a parasitic disease caused by infection with flatworms. Unsafe water and sanitation play a major role in transmission of the disease: the parasites need to transit through aquatic snails to complete their life cycle; populations who bathe, work or live near unsafe water are at major risk of infection, and the parasites' eggs can make their way into bodies of water when waste from infected individuals is not contained in adequate sanitation facilities, thereby perpetrating cycles of infection. In addition, a genital form of schistosomiasis, where the parasitic infection causes lesions in genital areas is likely to be a major risk factor for HIV infection in young adults. Therefore, there is a strong case for intensifying collaboration across the fields of schistosomiasis control, HIV control and WASH. In this *Infectious Thoughts* interview, the ISNTD speaks with Dr. Jutta Reinhard-Rupp (Head of the Merck Global Health Institute), Dr. Amadou Garba (World Health Organisation) and Dr. Vanessa Christinet (specialist in Female Genital Schistosomiasis at CIRES) and hears more about the strong rationale for HIV and schistosomiasis collaboration, the diversity of partnerships needed to accelerate and consolidate gains in NTD control and some of the research and technologies needed to fill current gaps.

There is a clear relationship between the Female Genital Schistosomiasis (FGS) patient cohort and high risk for HIV - what is that relationship?

Jutta Reinhard-Rupp (Merck): There is some discussion around the correct term that should be used as there exists "relationship, correlation, causality, association, plausibility" which all have slightly different meanings. In my opinion, the best description at the moment is to say there is a clear plausibility that urinary schistosomiasis and HIV prevalence's correlate in certain areas and age groups. Several papers have generated data that explain the plausibility (Feldmeier et al, 1995, Kjetland et al 2005, Jourdan et al. 2011, Kleppa et al 2014, many others) but a true causality can only be demonstrated in a longitudinal study which has not been done yet (missing funding, missing awareness etc.). The type of relationship/ plausibility is based on the following: Regarding the onset of FGS versus HIV, FGS normally starts earlier in life (i.e. genital lesions are already present providing an ideal entry point for the virus; even the respective receptor for HIV is overex-pressed in those lesions); observational studies have demonstrated that each infection with *S. haematobium* per 100 individuals is associated with a 2.9% relative increase in HIV infection; several mathematical modelling studies have shown such a correlation in HIV epidemics

Vanessa Christinet (CIRES): We have several elements that indicate that there may be a causal relationship between FGS and HIV. Several studies have shown an association, we have arguments for a temporal relationship and for a biological plausibility that FGS is a risk factor for HIV infection in women. Unfortunately a proper prospective study that could prove causality has not been conducted yet. This type of prospective studies needs a lot of resources and the field of schistosomiasis and FGS in particular is a neglected field of research, therefore such resources have not been invested yet. One way of studying risk factors are case control studies, which are less costly but less robust in terms of evidence.

Two case control studies have investigated if there were an association between urogenital schistosomiasis due to *S. haematobium* and HIV infection. They have shown a significant higher prevalence of HIV in women with uro-genital schistosomiasis compared to control women without uro-genital schistosomiasis. The results were highly significant with odd ratios up to 4. Confounding factors such as sexually transmitted infection were taken into consideration in these analyses (Downs et al., 2011; Kjetland et al., 2006). With these two studies we have some elements regarding the association between FGS due to *S. haematobium* and HIV.

Two studies have explored the HIV and *S. haematobium* epidemics in Sub-Saharan Africa. The first studied the two epidemics at the Sub-Saharan African level. It showed a correlation between the two epidemics with a higher prevalence of HIV in the highly endemic regions for *S. haematobium* (Ndeffo Mbah et al., 2013). The other one studied the two-epidemics at the national level in Mozambique (Brodish and Singh, 2016) and showed an increase odd of 3 after controlling for demographic and sexual risk factors.

The biological plausibility is based on the fact that FGS is responsible of lesion that alter the mucosal barrier on the cervix and which is associated with an increased risk of acquiring HIV. Moreover several studies have shown an increased concentration HIV target cells in the cervix in women with FGS compared with controls, which is another biological argument for an increased susceptibility to HIV of women with schistosomiasis. The temporal plausibility indicates that it is not HIV that is a risk factor for schistosomiasis as Schistosomiasis is mostly acquired early in childhood whereas HIV is acquired later in life for most infected women. I think we have high suspicion that schistosomiasis can be an important driver of HIV epidemic in Sub-Saharan Africa and I cannot understand how these elements can be occulted and neglected by the HIV researcher community.

Amadou Garba (World Health Organisation): In clear terms, the relationship between FGS and the risk for HIV means that women with FGS infection are at an increased risk of contracting HIV than those without. Consequently, preventing FGS in women makes them less susceptible to HIV, mostly in co endemic areas of sub Saharan Africa.

What do you hope to achieve by engaging the HIV community?

Jutta Reinhard-Rupp: FGS might be a completely underestimated factor contributing to higher HIV incidence rates in certain age groups of women. Without the HIV community knowing about this possibility (and genital lesions origin is difficult to determine), the underlying cause will continue to exist. Some HIV scientists became very interested when we talked about FGS as there are focal areas with very high HIV rates in women of 18-25y compared to the same age group in another area.

Vanessa Christinet: I think that normally HIV experts should be interested in determining vulnerability factors for Sub-Saharan women that is the population with one of the highest HIV incidence in the world (Kharsany et al., 2012). In international conferences on HIV prevention they present studies on the impact of certain aspect of vaginal flora and other factors for which we have very few objective implication on HIV infection but schistosomiasis never comes up as a possible factor although it is so frequent in Sub-Saharan Africa and although we have some patent elements of association. HIV community has much more resources that could allow conducting prospective trial investigating for example the early treatment of schistosomiasis on HIV incidence. If this strategy is one day proven to be effective, it would be a very cheap way of reducing HIV incidence and it would significantly show a reduction of the other disastrous impact of schistosomiasis on women's health.

Amadou Garba: FGS and HIV are co-endemic in many countries in Sub Saharan Africa. Given the association between FGS and HIV and considering the goal of UNAIDS of achieving zero new HIV infection by 2030, there is a need to increase the awareness about the increased risk of women with FGS face and support FGS prevention through preventive chemotherapy for schistosomiasis. We are also advocating for FGS to be part of an integrated health delivery package for women in endemic areas. Women who suffer from FGS usually complain about pain, bleeding and often infertility. But there is low level of awareness even among medical practitioners in most schistosomiasis endemic settings. Clinical awareness of FGS can facilitate and enable diagnosis during consultation for STDs, cervical cancer or HPV. We should ensure the presence of integrated approaches for the detection, prevention and treatment of FGS.

A lot of work is currently ongoing to develop a pediatric formulation for praziquantel (PZQ) - what limitations to do you foresee when it comes to treatment of cases and how will these relate to FGS disease burden?

Jutta Reinhard-Rupp: In the beginning of providing access to the new pediatric formulation, children need to be tested which could provide an obstacle. Only with a safety database (to be set-up in the first years), the program can convert to MDA (mass drug administration). Treating young girls regularly and early on (with the pediatric praziquantel, you can start as of 3 months of age), you are lowering the risk of heavy and constant infections that may lead to early FGS symptoms in girls at primary school age. No data exists for the potential use of PZQ in patients already suffering from FGS – how to treat the lesions is currently unclear.

Vanessa Christinet: I am personally not working on a pediatric formulation but I know that, as seen before,

children get infected very early in life even when they are babies, when the mother is cleaning them in infested water. A pediatric formulation could help treating young girls at an early stage before chronic lesions appear in the reproductive organs, which are much more difficult to treat. It would also prevent other chronic hepatic or renal diseases due to the parasite.

Amadou Garba: Children below 5 years of age represent a group at risk for schistosomiasis. But this age group is currently is not targeted for treatment through preventive chemotherapy due to the absence of a suitable and appropriate pediatric praziquantel (PZQ) formulation. WHO supports initiatives to develop such suitable pediatric formulation that can include children of this age group in mass treatment campaigns.

As in many other NTD settings, it is highly apparent that pharmacological intervention on its own will not be enough. Given this, where are the current gaps in coverage?

Jutta Reinhard-Rupp: The difficulty with schistosomiasis is its dependency from an intermediate host (snails), the water contact and the missing sanitation and awareness (it is a silent disease in most cases). Consequences of schistosomiasis are more chronic in nature and can develop many years later, after infection. Drug treatment only will not eliminate the disease but will support the control of the disease morbidity.

Vanessa Christinet: I am not an expert in this field but it seems quite obvious that awareness is lacking. The lake of awareness concerns the affected populations, but also concerns the medical staff and the political leaders in charge of public health programs and policies. It is probably due to the fact that the consequences of the disease appear much later in life and the causality between the infection and the associated pathologies is not easily provable and understandable by the populations. If awareness is increased, then a strategy should not be only based on treatment but also on treating the cause, eliminating the snails, and including preventive measure for the populations.

Amadou Garba: Preventive chemotherapy with praziquantel is the main strategy recommended by WHO to control the morbidity due to schistosomiasis. WHO recommends regular treatments of school aged children, occupational groups at risk up to the whole community according to the prevalence of the disease. The objective is to treat at least 75% of all school aged children in all moderate to high burden areas by 2020 according to the NTD road map. To date tremendous progress has been made, with coverage rate for school-age children doubling in 5 years, from 26% in 2012 to 52% in 2016. However WHO is pursuing efforts to expand treatment to non-treated endemic countries. The major gaps include: (i) an absence of a pediatric formulation that can allow preschool aged children into mass treatment campaigns; and, (ii) the current donation of praziquantel does not provide for the treatment of at-risk adults. In addition to preventive chemotherapy, programmes should improve water, sanitation and hygiene (WASH) services, initiate snail control and promote health education and behavioural change.

Given the gaps that you have highlighted, who do we need to engage with on a priority basis - short, mid and long term? Would there be any 'call to action' from you towards these disciplines?

Jutta Reinhard-Rupp: Currently, the GSA (Global Schistosomiasis Alliance) is a platform that is supporting the global community in addressing those topics and actions that are needed to eliminate the disease on a long term. For schistosomiasis, we need investment in better diagnostics, improved tools for vector control and water & hygiene. On a longer term, one has also to consider to invest in alternatives to PZQ (new drug discovery and vaccines)

Vanessa Christinet: I think I am not an expert in that field and I prefer to let the expert answer precisely to this question. But the first step would necessitate a political will and should target increasing awareness of the affected population on the health related problems due to schistosomiasis and how to avoid it.

Amadou Garba: In the short term we need more donated praziquantel and additional funding to deliver and treat everyone in need, including school populations and adults. For this, enhanced donor support is required. Furthermore, the search for a suitable pediatric formulation of praziquantel should be accelerated. For the longer term and for sustainable control and elimination of schistosomiasis, countries should implement a comprehensive integrated strategies, including preventive chemotherapy, WASH, health education and snail control.

Digital Healthcare has started to make inroads into NTD settings - could this enabling approach assist in your effort?

Jutta Reinhard-Rupp: Absolutely – we are relying on very thin mapping data which leads to a lot of overtreatment with PZQ (“healthy” children at school are

treated) while at the same time, the overall drug amount is not sufficient to treat all patients infected or at risk (most often, no adult treatment possible). A more precise mapping approach could be supported by digital tools.

Vanessa Christinet: Digital Healthcare could play a role especially in the diagnosis of FGS. A research team in South Africa has investigated a possibility of making the diagnosis of FGS based on digital images of cervix (Holmen et al., 2015a, b). The results are really promising and it could help to train and assist clinician on the diagnosis which usually necessitate elaborate technology to confirm the pathology (anatomo-pathology, PCR,...) which are rarely available in remote area and not affordable for most of the patients. In our project in Cameroon, we would like to establish an e-health platform with various experts (gynecologists, infectiologists, expert in FGS, etc) to assist the local clinician with the diagnostics on various pathology of the cervix. Studies have shown that high-resolution pictures of the cervix can be as good as colposcopy and could enable to diagnose cervical cancer, dysplasia, schistosomiasis, etc.

Amadou Garba: Positively, digital healthcare can assist in the surveys data collection and reporting as well as in monitoring the safety of treatment and the accurate reporting of mass drug administration coverage. More specifically on FGS, it can be used to sensitize women about the disease and contribute towards prevention and promote better disease awareness among health workers.

What role if any is there for the local patient advocacy initiatives?

Jutta Reinhard-Rupp: I'm not aware of dedicated patient advocacy groups for NTDs, but if there were those groups, it would be of utmost importance to mobilize them. Missing awareness of the disease (at patient and governmental level) is a critical issue which hinders the overall elimination agenda.

Amadou Garba: Local advocacy initiatives are important as they support information campaigns in affected communities, including strategies of prevention. The more people are informed about the disease, the better the rate of compliance among affected communities.

Can the 'child's right to healthcare' be used as a new vehicle to engage child-parent cohorts? Can this be used to lobby the governance in endemic countries or perhaps even regionally?

Jutta Reinhard-Rupp: It would be a great approach but we need to understand how these initiatives would work in most rural settings of Sub-Saharan countries. I have no experience to advice on that topic.

Amadou Garba: The right to healthcare is a basic human right. WHO's mandate is to build a better, healthier future for people all over the world. In the case of schistosomiasis control and elimination, by supporting initiatives for a paediatric formulation and in promoting awareness about FGS, WHO is fully playing its part in creating conditions to achieve universal health coverage. In tackling FGS, we are addressing targets set for SDG3 – "By 2030, ensure universal access to sexual and reproductive health-care services, including for family planning, information and education, and the integration of reproductive health into national strategies and programmes" and "By 2030, end the epidemics of AIDS, tuberculosis, malaria and neglected tropical diseases and combat hepatitis, waterborne diseases and other communicable diseases". This is added motivation for governments to invest in prevention of FGS.

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