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'Female Genital Schistosomiasis: Translational Challenges and Opportunities' – outputs and actions from a consultative, collaborative and translational workshop

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Abstract

Female genital schistosomiasis (FGS) is a chronic disease manifestation of the waterborne parasitic infection *Schistosoma haematobium* that affects up to 56 million women and girls, predominantly in sub-Saharan Africa. Starting from early childhood, this stigmatizing gynaecological condition is caused by the presence of *Schistosoma* eggs and associated toxins within the genital tract. *Schistosoma haematobium* typically causes debilitating urogenital symptoms, mostly as a consequence of inflammation, which includes bleeding, discharge and lower abdominal pelvic pain. Chronic complications of FGS include adverse sexual and reproductive health and rights outcomes such as infertility, ectopic pregnancy and miscarriage. FGS is associated with prevalent human immunodeficiency virus and may increase the susceptibility of women to high-risk human papillomavirus infection. Across SSA, and even in clinics outside endemic areas, the lack of awareness and available resources among both healthcare professionals and the public means FGS is underreported, misdiagnosed and inadequately treated. Several studies have highlighted research needs and priorities in FGS, including better training, accessible and accurate diagnostic tools, and treatment guidelines. On 6 September, 2024, LifeArc, the Global Schistosomiasis Alliance and partners from the BILGENSA Research Network (Genital Bilharzia in Southern Africa) convened a consultative, collaborative and translational workshop: 'Female Genital Schistosomiasis: Translational Challenges and Opportunities'. Its ambition was to identify practical solutions that could address these research needs and drive appropriate actions towards progress in tackling FGS. Here, we present the outcomes of that workshop – a series of discrete translational actions to better galvanize the community and research funders.

Research Article

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Introduction

Female genital schistosomiasis (FGS) is a neglected, parasitic, gynaecological disease affecting both women and girls in sub-Saharan Africa (SSA) that is underreported, misdiagnosed and poorly treated (Bustinduy et al., 2022). It is estimated to affect between 30 and 56 million women and girls, predominantly in SSA countries, although this is likely to be an underestimate of the actual burden of disease given the lack of adequate community surveillance (Ndubani et al., 2024).

FGS is a gender-specific chronic manifestation of urogenital schistosomiasis, a disease caused by exposure to the freshwater larvae (cercariae) of water-borne parasites of the *Schistosoma* genus, primarily *Schistosoma haematobium*. After penetrating the body via the skin, the *S. haematobium* larvae mature into adults and live in the venous blood vessels of the urogenital system, where the females produce eggs. Whilst a proportion of these eggs are excreted in urine, some eggs become trapped in urogenital tissues, triggering a localized inflammatory response that can progress to the formation of granulomas and irreversible fibrosis (Buonfrate et al., 2025). It is this chronic manifestation of schistosomiasis that typifies FGS and causes debilitating morbidity and adverse reproductive outcomes such as infertility, ectopic pregnancy and miscarriage (Rossi et al., 2024; Lamberti et al., 2024a). FGS is associated with prevalent human immunodeficiency virus (HIV), *Trichomonas vaginalis*, and may increase the susceptibility of women and girls to high-risk human papillomavirus (HPV) infection, the latter being a well-characterized risk factor for cervical cancer (CC) (Kjetland et al., 2006b, 2010; Downs et al., 2017; Sturt et al., 2020a, 2021, 2025).

FGS has a considerable impact on affected women's quality of life, causing symptoms including vaginal discharge, vaginal itching, post-coital bleeding and abdominal pain. The similarity of these symptoms to sexually transmitted infections (STIs) leads to inaccurate diagnosis and treatment as well as stigma (Ndubani et al., 2024; Rossi et al., 2024).

The World Health Organization's (WHO) public health guidelines for schistosomiasis do not specifically include FGS, and treatment recommendations are an extension of those for schistosomiasis infection. This includes mass drug administration (MDA) of the anti-helminth drug, praziquantel (PZQ), in endemic regions (>10% prevalence) (World Health Organization, 2022). There is currently little evidence that PZQ is effective for treating or reversing the lesions associated with FGS, which are mostly chronic manifestations of the disease. However, initiating PZQ treatment early in life and maintaining this treatment strategy throughout childhood and adolescence can prevent lesions from establishing in the first place (Richter et al., 1996; Kjetland et al., 2006a; Downs et al., 2013; Arenholt et al., 2024; Kabengele et al., 2024). FGS is not included in the global burden of disease estimates for schistosomiasis, hindering the estimation of disability-adjusted-life-years (DALYs), and the absence of data relating specifically to the FGS burden has substantial implications for its management and efforts to introduce control strategies (Lamberti et al., 2024b).

Although FGS has long been neglected, there is building momentum to include this condition on the agenda of research funders, policymakers and community health workers (Ainsworth, 2024). In 2019, the Coalition for Operational Research on Neglected Tropical Diseases (COR-NTD) partnered with the European Congress on Tropical Medicine and International Health to convene a meeting of international experts to identify research priorities for FGS (Engels et al., 2020). While there are no standardized methods for population-based screening and diagnosis of FGS, COR-NTD are currently undertaking a multi-country assessment of prevalence for FGS (MAP-FGS) that is enrolling over 9,000 women and girls aged 15–60°years across 6 countries (Table 1). This study aims to determine the prevalence of FGS across 6 SSA countries to provide quantitative evidence of burden. While there may be wider operational impacts of the recent USAID funding pause on national neglected tropical disease (NTD) programmes, the MAP-FGS study was funded by alternative means and therefore continues to progress.

The FGS Integration Group is a coalition of organizations that aims to raise awareness of FGS by galvanizing joint action across sexual and reproductive health and rights (SRHR), HPV/CC, HIV, NTD and water, sanitation and hygiene (WASH) sectors. WASH programmes allow the provision of fresh, clean water and adequate menstrual hygiene management, which are essential for the management of FGS (Stothard et al., 2020; Mazigo et al., 2021; Mwinzi et al., 2025). In Zambia, the Zipime Weka Schista study is empirically testing an integrated diagnostic approach for these connected conditions, both at community and clinic levels (Shanaube et al., 2024). In 2022, the BILGENSA Research Network (Genital Bilharzia in Southern Africa) was set up as a collaborative multidisciplinary network to advance clinical research on female and male genital schistosomiasis across Southern African endemic countries. The network launched with a 2-day workshop in Lusaka in 2022, during which stakeholders mapped the status of FGS research and development (R&D) and clinical care and identified research priorities and needs in FGS. These included the need to raise awareness, improve diagnostic capabilities, develop treatment guidelines, integrate SRHR screening strategies and improve surveillance. Outcomes from the workshop were made publicly available in the BILGENSA Research Network Report (Ndubani et al., 2024).

Building on this foundational work, LifeArc, the Global Schistosomiasis Alliance (GSA) and partners from the BILGENSA Research Network convened a collaborative, translational workshop: 'Female Genital Schistosomiasis: Translational Challenges and Opportunities' in September 2024. The aim was to foster further consultations, enhance stakeholder networking and identify translational solutions within reach that address the research needs and priorities already identified. As several previous papers have already articulated the overarching research needs and priorities for tackling FGS (Ndubani et al., 2024; Rossi et al., 2024; Lamberti et al., 2024b; Mwinzi et al., 2025; Trust, 2025), this report summarizes the translational actions identified in this joint collaborative workshop.

The workshop

The hybrid workshop, titled 'Female Genital Schistosomiasis: Translational Challenges and Opportunities', involved 79 participants, representing 11 African countries, 7 European countries and 3 locations in North America. Attendees met in London and were joined by colleagues online. Moderated discussions focused on the below themes during which participants had the opportunity to put forward actions and solutions for FGS that would be scalable across SSA:

(1) Community, capacity strengthening and health economics
(2) Therapeutics and novel treatment targets

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Table 1. Pilot research projects seeking to (1) improve and validate diagnosis for FGS alone and/or in combination with other infections and (2) improve awareness of FGS and/or integrate FGS training and healthcare into existing services

Project	Country	Description	Aim
FGS Accelerated Scale Together (FAST) package	Madagascar and Ghana	The FAST package combined proven interventions in training, MDA, diagnosis and treatment and community awareness to address FGS in 4 districts in Ghana and Madagascar. Interventions included online and in-person healthcare provider training, an Educators' booklet to create awareness among teachers, healthcare professionals and the community, and advocacy for the provision of PZQ in primary care (Krentel et al., 2024). https://fastpackage.org/	1. Increased awareness of FGS in the health system, medical training and at the community level. 2. Development of online and in-person training packages. 3. In-person training for frontline healthcare workers at the district level.
COUNTDOWN	Liberia and Nigeria	COUNTDOWN conducted health system strengthening research aimed at building the capacity of the health system to manage cases of FGS among young girls and adult females living in schistosomiasis-endemic regions. The research employed participatory health research methods to engage health system actors at various levels of the health system (including frontline health workers, Consultant Gynaecologists, Consultant Public Health Physicians and NTD programme implementers at LGA, State and National levels) to collaboratively develop and pilot FGS case management intervention tools at the primary health care level in schistosomiasis-endemic regions. https://countdown.lstmed.ac.uk/	1. Increased awareness of FGS in the health system, medical training and at the community level. 2. Development of online and in-person training packages.
ZAMBART, Zipime-Weka-Schista study (Do self-testing sister!)	Zambia	The 'Schista!' study aims to integrate FGS within the wider SRHR screening strategies by using home self-sampling for the screening of FGS alongside HPV and self-testing for HIV and STIs and comparing this with clinic-based testing, with a special emphasis on health economics (Shanaube et al., 2024). https://www.zambart.org.zm/2023/10/03/the-zipime-weka-schista-study/	1. Longitudinal cohort study aiming to enrol 2,500 non-pregnant, sexually active and non-menstruating women aged 15 − 50 years from 2 districts in Zambia, with 2 years of follow-up. 2. Study to assess if the integration of home self-sampling for the screening of FGS, high-risk HPV, HIV and STIs is a diagnostically accurate, cost-effective and self-empowering strategy that will increase the detection of cases.
Côte d'Ivoire Ministry of Health and Unlimit Health	Cote d'Ivoire	Integration and scaling up of prevention services to determine the processes and resources needed for sustainable integration. Results from 2 districts will inform evidence-based guidelines for the national FGS strategy (Preston et al., 2023). https://unlimithealth.org/research/fgs-research-cdi/	1. To measure if the integration of FGS preventive treatment into different routine health services can reach at-risk women (15 − 29 years old). 2. To evaluate if training and resources enhance awareness of FGS among health workers and at-risk women (15 − 29 years).
LVCT Health Minimum Services Package (MSP)	Kenya	Integration of FGS within SRHR services in the Kenyan public health system. Development of a minimum service package that seeks to enhance health literacy among health workers and their managers to ensure the health system is prepared to integrate FGS in 3 counties in Kenya. https://lvcthealth.org/fgs/	1. Develop guidance for, implement and evaluate the integration of HIV/FGS and SRHR services. 2. Evaluate the acceptability, feasibility and cost-effectiveness of FGS and SRHR service integration.
Multi-country Assessment of Prevalence for Female Genital Schistosomiasis (MAP-FGS) Study	Ghana, Mali, Madagascar, Nigeria, Senegal and Tanzania	Determine the prevalence and severity of FGS to provide quantitative evidence of its burden. The study is enrolling over 9,000 women and girls aged 15 − 60 years across 6 countries. https://www.cor-ntd.org/female-genital-schistosomiasis	1. To estimate the prevalence of *confirmed* FGS cases in women aged 15 – 60°years across different *S. haematobium* archetypal settings in SSA. 2. To quantify the severity of FGS among *confirmed* cases in women aged 15 – 60°years. 3. To identify feasible, accurate and locally tailored diagnostic algorithms and screening procedures for diagnosing FGS without the use of colposcopy.
Multi-country training and diagnosis of FGS DUALSAVE-FGS	South Africa, Mozambique and Eswatini	Cost-effective joint screening method for FGS and cervical cancer. https://fgsnomore.org/	1. Clinically validate the Spectral Artificial Vision (SAVE) colposcope, a low-cost, hand-held digital colposcope. 2. Virtual training of frontline primary health care professionals and gynaecologists in FGS diagnosis and management.

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Table 2. Summary of translational actions from across the themes discussed

	Community, capacity and health economics	Therapeutics and novel targets	Diagnostics: visual and laboratory
The problem	Limited awareness of FGS in affected areas, even among clinical staff. The similarity of these symptoms with STIs leads to inaccurate diagnosis and treatment, as well as stigma.	There is no specific treatment for FGS, only praziquantel (PZQ) is used to kill adult worms. Evidence of the effectiveness of PZQ in FGS is lacking, and no alternative treatment exists.	There is no standardized protocol for diagnosing FGS. Current approaches, both visual and laboratory, have limitations.
Recommendations	1. Engage with Ministries of Health and Education, as well as FGS care providers, to improve awareness in affected communities by: • Standardizing school and clinical curricula. • Creating FGS health messaging and disseminating it through platforms. 2. Improve reporting processes to collect routine FGS diagnostic data for estimations of disease burden and prevalence. 3. Integrate FGS screening and pilot the inclusion of FGS into cervical cancer and sexual and reproductive health and rights (SRHR) clinics. Create cost and cost–effectiveness analysis data packages.	1. Create standardized FGS case definitions (molecular, visual and symptomatic) and clinically relevant endpoints and outcome measures. 2. Create data packages from existing MDA programmes to assess their impact on population-level prevalence and pathology. 3. Conduct a longitudinal study of PZQ treatment regimens on FGS, including the assessment of novel targets for therapeutic development. 4. Conduct repurposing studies to assess the efficacy of existing drugs for managing FGS.	*All diagnostics*: Define standardized reference tests for FGS, with severity scores and protocols for data capture and processing. *Visual diagnostics*: 1. Review diagnostic infrastructure and map the availability of colposcopes. 2. Update the WHO FGS Pocket Atlas to guide colposcopy exams. 3. Create a colposcopy image bank for machine learning development. *Laboratory diagnostics*: 1. Develop a molecular point-of-care test to detect schistosomiasis DNA from suitable samples along with guidelines to improve the use of existing tests.

(3) Diagnostics – laboratory/field and visual examination

During the workshop, discussions on diagnostics were separated into laboratory/field and visual (gynaecological examination) but have been combined for the purposes of this report. This article describes the translational actions and opportunities, reached through discussion and consensus by stakeholders, which aim to guide the development of new and improved solutions for tackling FGS.

Translational actions and opportunities identified in the workshop

All thematic discussions generated a range of potential actions and solutions to address FGS at a global, national, regional and community level. Under each theme, the following is presented and summarized in Table 2:

(1) The *problem* to be solved: these were highlighted during the discussions.
(2) The *endpoint objective* being worked towards: these were identified after the discussions.
(3) The *translational actions and recommendations* and context surrounding them that could help to deliver these endpoint objectives.
(4) *Key points* from the workshop discussion that provide context to support these actions.

It is hoped that these translational actions will be taken up and implemented by communities and collaborators, ensuring the delivery of projects that allow the integration of FGS healthcare into existing services (see examples in Table 1). With limited funding, this implementation may be challenging, but if supported by governments in affected countries, private healthcare systems and non-governmental organizations (NGOs), then the delivery of specific shared endpoint objectives remains achievable.

Community, capacity strengthening and health economics

Problem

The signs and symptoms of FGS are similar to those associated with STIs, making diagnosis challenging for both community health workers, those within primary care and women living with FGS. Moreover, as FGS awareness at the clinical and community level is poor, the index of suspicion for FGS among healthcare professionals is low, and the disease is often incorrectly diagnosed. STI-like symptoms are associated with stigma and discrimination, and women living with FGS may experience delays in seeking and accessing care. Health systems are not primed to provide FGS-related care, limiting community-health worker efforts to access a functional FGS care cascade. This is exacerbated by limited information at the community level on the burden of FGS. Further, outside MDA programmes, which primarily focus on school-aged children, access to PZQ in the health system remains inadequate. The economic impact of FGS is also not quantified, hindering the adequate allocation of direct healthcare resources towards effectively preventing, diagnosing and treating the disease at the earliest opportunity.

Endpoint objective

There is greater awareness of FGS in endemic areas across all levels of clinical practice and throughout affected communities. Women can access FGS-related healthcare, including diagnosis, personalized information and treatment, through established health programmes that prioritize affordable and cost-effective prevention and control strategies.

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Translational actions

(1) Engage with the Ministries of Health and Education, and those providing care for women and girls with FGS in affected countries, to agree on a strategic approach to:
   (a) Create standardized school and clinical curricula to improve FGS awareness among affected communities and within the medical profession for its prevention, diagnosis and treatment.

There have been multiple small-scale projects focusing on FGS training for healthcare workers (Table 1). Despite these efforts, awareness of FGS remains low, and it remains necessary to engage further with Ministries of Health and Education in affected countries. Existing training curricula, which may include SRHR, STI and HIV policies and guidelines, need to be adapted to incorporate content on FGS for the education of medical students so that health workers conducting visual exams can differentiate between STIs, cervical (pre-)cancer and FGS. The training curricula should also address FGS management, allowing health workers in endemic areas to recognize disease symptoms so that women and girls can be diagnosed, referred and treated. This would also serve to break down misconceptions and myths surrounding FGS, such as the belief that it is an STI (Wambui et al., 2024).

   (b) In collaboration with local communities in endemic areas, create public health messaging on FGS and disseminate it through multiple platforms to improve awareness across multiple ages and groups.

Awareness-building activities should include highly targeted messaging to key community subgroups, recognizing that schoolgirls, women of reproductive age and older women may engage in different activities. These activities may be facilitated by community health workers, for example, as piloted in Liberia and Nigeria through the Calling Time for Neglected Tropical Diseases (COUNTDOWN) research programme (Table 1). Here, case management intervention tools that included operational manuals and a signs and symptoms FGS scorecard were codeveloped and assessed at the primary health care level (Nganda et al., 2023). Similarly, workshop participants reported that drama groups in Malawi, Tanzania and Zambia have been employed to engage communities through culturally appropriate dissemination events. Other methods include the use of different social media tools that may be utilized to educate and inform the public with verified and accurate information on FGS. It is necessary to ensure that men are included to address the discrimination and stigma associated with FGS, as well as to inform them that they may also be affected by male genital schistosomiasis (Bustinduy et al., 2022). For example, a pilot study in Tanzania has involved men in promoting care for FGS after surveys identified the important role of men in ensuring women with FGS seek medical advice (Lambert et al., 2024). Lessons can also be learned from the HIV field, where communities led health literacy efforts and emphasized the importance of pre-exposure prophylaxis (Young and Valiotis, 2020).

(2) Develop reporting processes to collect routine FGS diagnostic data that may be used to estimate disease burden and prevalence, allowing sufficient and proportional PZQ allocation and distribution.

There are currently no standardized methods for population-based FGS screening and diagnosis. The MAP-FGS project is aiming to address this by generating data on FGS prevalence across 6 countries, particularly among girls and women aged 10–60 years (Table 1). The collection and centralized reporting of routine diagnostic data would help improve understanding of FGS morbidity and prevalence. This would, in turn, allow improved PZQ allocation and distribution to primary healthcare facilities and potentially help estimate the FGS burden using DALYs. Furthermore, the knowledge gained from MAP-FGS may inform further data collection processes and research studies that will help support integrating FGS care into broader SRHR services.

(3) Pilot the integration of FGS screening and management into CC and SRHR services. Create cost and cost–effectiveness analysis data packages to aid with the scalability of FGS screening programmes.

As mentioned, the Zipime-Weka-Schista study (Shanaube et al., 2024) has pioneered the integration of multi-pathogen screening in Zambia and includes an economic analysis providing data on the cost-effectiveness of home-based compared with clinic-based procedures (Table 1). However, to be generalizable to routine care in all endemic areas, other countries should contribute similar data, captured via standardized reporting tools to ensure information can be reported for all diseases on a single platform. To inform health policy, cost–effectiveness and economic analyses to compare the costs and benefits of FGS control strategies are essential when allocating resources. This would allow the estimation of the affordability of different control strategies to support priority setting in resource-scarce environments. Given that integration of FGS into existing health services would require further management and resources, it must be determined if the health services are ready to accommodate integration. To facilitate this work and to develop pilot studies, it will be beneficial to develop a framework and health decision analytical model to evaluate the cost-effectiveness of FGS screening strategies (Lamberti et al., 2024b). Data packages drawn from pilot projects to integrate FGS with CC and SRHR services may capture data from different integration models, including costs to patients such as travel costs and direct medical expenses. These data may further help estimate the FGS burden using DALYs.

Therapeutics and novel targets

Problem

There is no specific treatment for FGS. Currently, in schistosomiasis-endemic areas, PZQ is distributed to allow the preventive treatment of school-aged children and high-risk groups with PZQ through MDA programmes (World Health Organization, 2022). Outside of these programmes, women and girls with suspected FGS may be treated with a single dose of PZQ (World Health, 2015). However, PZQ targets and kills the adult *S. haematobium* worms, but there is limited evidence assessing its effectiveness in resolving characteristic cervicovaginal lesions or reducing FGS-associated morbidity (Kjetland et al., 2006b; Downs et al., 2013; Bustinduy et al., 2022; Arenholt et al., 2024; Kabengele et al., 2024). Additionally, as PZQ demonstrates a lack of activity against juvenile worms, such as the schistosomulum stage, and there are few alternative treatments, there is an urgent need to identify novel evidence-based treatments for FGS that can effectively kill the parasite in all life stages or reduce FGS-associated morbidity. However, the development of new treatments is hindered by a lack of commercial return of investment, objective

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efficacy endpoints, animal model data and identification of sensitive and specific FGS biomarkers to monitor treatment efficacy. Furthermore, PZQ does not prevent reinfection if there is at-risk water contact following administration of treatment.

Endpoint objective

Clinical recommendations for the use of FGS treatments are available based on standardized data sets with specific therapeutic endpoints. Targets for alternative parasite-directed and/or host-directed treatments for FGS have been identified and assessed.

Translational actions

(1) Create a working group to standardize FGS case definition(s) (molecular, visual and symptomatic), clinically relevant endpoints and outcome measures.

It is necessary to standardize FGS case definitions, focusing on whether FGS is defined by specific FGS pathology (e.g. cervicovaginal lesions), the detection of *Schistosoma* DNA or eggs in the genital tract and/or the occurrence of clinical symptoms. Circulating anodic antigen (CAA), urine microscopy and urine *Schistosoma* polymerase chain reaction (PCR) are tools used to diagnose active *Schistosoma* infection, but they do not evaluate FGS status. Thus, resolution of urinary *S. haematobium* infection, confirmed by negative urine microscopy, the absence of CAA or *Schistosoma* DNA in the urine and/or stool, should not be the clinical endpoint for FGS treatment. Instead, negative genital *Schistosoma* PCR, resolution of FGS cervicovaginal lesions and/or sustained reduction of symptoms would be prioritized as endpoints. This is especially important if lesions cause morbidity (e.g. abnormal bleeding and pain) or render a patient vulnerable either to HIV or HPV. Different stages and clinical manifestations of FGS which may require different treatment and confounders such as STIs should be considered to ensure lesions are not caused or aggravated by a coinfection.

(2) Create data packages from existing MDA programmes to assess their impact on population-level FGS prevalence and pathology, along with correlations to additional medical treatments.

Published research has emphasized the need for sustained treatment with PZQ from early life through to adolescence to prevent FGS lesions from establishing (Arenholt et al., 2024). For example, a prospective study in Zimbabwe found that women who had undergone PZQ treatment in their childhood years had 50% less contact bleeding and lesion sizes compared to those who had never received treatment (Kjetland et al., 2008). In Kenya, girls and women who had received PZQ through MDA before the age of 21 were less likely to develop sub-fertility in later years (Miller-Fellows et al., 2017).

PZQ MDA to school-aged children has been in place in most countries since 2001, meaning that many women who are now in their mid-20s and 30s have received preventative chemotherapy (Rossi et al., 2024). As such, there may be a wealth of data available from patient records in endemic areas that may be reviewed to better understand FGS prevalence and associated symptoms. Additionally, this may allow researchers to identify correlations and ascertain key information relating to the use of other medications for co-morbidities (e.g. antibiotic therapy). Developing this understanding may help improve the treatment of FGS lesions using existing medications.

(3) Conduct a sufficiently powered, longitudinal study to assess the effectiveness of PZQ treatment regimens on FGS, including the assessment of novel targets for therapeutic development.

Some studies have highlighted that PZQ can lead to a marginal improvement for women who have FGS, with treatment decreasing lesion severity. Women who presented with less severe baseline disease were associated with FGS lesion resolution post-treatment (Kabengele et al., 2024). A randomized controlled trial aiming to assess the efficacy and safety of a repeated PZQ-dosing regimen was recently conducted, comparing single-dose treatment of PZQ to 5 doses over 10 weeks. This study found an insignificant reduction in abnormal blood vessels only following treatment with PZQ, although treatments did result in reductions in worm populations, pelvic exam abnormalities and urogenital complaints. The repeated regimen seemed more effective at eliminating the dwelling worm population than the single-dose regimen (Arenholt et al., 2024). Some important limitations of the trial included a very small number of adequate images reviewed and a lack of age stratification of results, potentially overlooking the differences in the natural history of FGS through time. The lack of adjustment on age-related morbidity differences limits its generalizability to all girls and women with FGS across settings.

Research has shown that inflammation occurs around eggs situated in the genital mucosa where fibrotic or chronic inflammatory lesions form, and treatments must be able to target this later stage of disease (Jourdan et al., 2011; Randrianasolo et al., 2015). Further studies should be undertaken to determine the effectiveness of using PZQ for FGS treatment, considering age, confounding variables and the assessment of alternative treatments that may resolve chronic cervical lesions with established abnormal blood vessels. Longitudinal studies may include genomics/transcriptomics analysis of women with molecular and visual FGS, before and after treatment, to identify novel therapeutic targets at different time points/stages.

(4) Conduct drug repurposing studies to assess the efficacy of existing drugs for FGS.

Repurposing of existing approved drugs may offer a safe, rapid and cost-effective alternative to early-stage drug discovery. Potential candidates for drug repurposing include non-steroidal anti-inflammatories, corticosteroids and anti-fibrotics. Used in combination with PZQ, these drugs may help alleviate FGS symptoms. Additionally, treatment with a combination of the antimalarial drugs artesunate and mefloquine was as effective against urinary *S. haematobium* infection as PZQ (Bottieau et al., 2024). However, while repurposing drug studies may be advantageous, careful consideration must be given to any medication that may interact with PZQ's pharmacokinetic and pharmacodynamic performance (e.g. corticosteroids or tuberculostatics) (Ridtitid et al., 2002; Jauréguiberry et al., 2010).

Diagnostics – laboratory/field and visual

Problem

Conventional FGS diagnosis involves visual inspection of the cervicovaginal mucosa, typically with the aid of a colposcope, to visually detect lower genital tract lesions suggestive of FGS (Søfteland

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et al., 2021; Bustinduy et al., 2022). While biopsy of these lesions to detect parasite eggs is considered the gold standard for FGS diagnosis, it is not widely used as the approach is invasive, and there are theoretical concerns regarding HIV transmission among sexually active women (Poggensee et al., 2001; Wright et al., 2001; Kjetland et al., 2009).

To facilitate clinical diagnosis of FGS, the WHO developed a visual pocket atlas for providers performing colposcopy (World Health Organisation, 2015). There are 4 classic lesions associated with FGS that correspond to *Schistosoma* egg deposition in the mucosa. These identified lesions (homogeneous yellow sandy patches, grainy sandy patches, abnormal vessels and rubbery papules) can be accompanied by surface bleeding and/or other signs of inflammation or scarring. Lesions may be large or small on all cervicovaginal surfaces, including vaginal walls, but are most often discovered on the cervix due to current clinical training, CC screening programmes and colposcope design (Søfteland et al., 2021). Most FGS studies have naturally been conducted in endemic areas. Therefore, *S. haematobium* ova may have been deposited continuously from childhood until the investigation date, presenting a range of recently established lesions and chronic manifestations. Furthermore, depending on the localization of the egg deposition, lesions may not be visible if eggs are deposited in the upper genital tract (Bustinduy et al., 2022).

It is important to note that there is no standardized training method to correctly identify FGS-associated cervicovaginal lesions. This is compounded by the expense and limited availability of colposcopes (standard and handheld), which means that visual FGS diagnosis tends to be limited to research settings (Søfteland et al., 2021). Where colposcopy is used, there is evidence of high inter-user variability, and there may be issues with sensitivity where eggs embedded in inaccessible parts of the genital mucosa are missed (Sturt et al., 2023). In addition, there are confounding gynaecological diseases with similar visual presentations to FGS, and heterogeneity within a healthy cervix, limiting the accuracy of visual readings in correctly identifying each condition.

Alternative laboratory diagnostic approaches suitable for use in low-resource settings should be considered to aid the clinical diagnosis of FGS and determine the severity of infection. Diagnostics for detecting *S. haematobium* eggs/antigens in urine/serum as a measure of active infection can act as a proxy marker for FGS (e.g. CAA; Corstjens et al., 2014) or DNA in urine and/or stool by PCR (Pillay et al., 2020). However, approximately 40% of females with genital schistosomiasis do not have eggs detected in urine (Poggensee et al., 2001; Kjetland et al., 2005; Hegertun et al., 2013). In addition, these methods suffer from an inability to detect dead parasite eggs embedded within genital tissue so women may be found to have FGS lesions based on a visual examination, but test negative using urine microscopy (or other molecular tests). An affordable point-of-care (POC) molecular test demonstrating high sensitivity and specificity, or a diagnostic method that can specifically detect visual FGS, has yet to be developed.

No single diagnostic tool will provide an accurate and scalable solution to allow the identification of FGS. Instead, a combination of visual and laboratory tools, together with algorithms to support healthcare professionals' decision-making, will be necessary for the specific diagnosis of FGS across all endemic regions. A WHO target product profile for FGS diagnostics is being developed but has yet to be finalized.

Endpoint objective

Alternative or improved diagnostic tools for FGS have been developed and properly validated.

Translational actions

For all diagnostics (visual and laboratory/field)

(1) Create working group(s) to define the following:

(a) Standardized reference test(s) for FGS, preferably with severity scores.

As routine lesion biopsy may be seldom available in endemic settings, it is essential that an accessible gold-standard reference test is defined. Additionally, there is a need for the development of additional diagnostics that may form part of an FGS testing algorithm. As demonstrated by the COUNTDOWN research programme and a research study in Tanzania, questionnaires can be used to assess symptoms, although these demonstrate high sensitivity but low specificity (Nganda et al., 2023; Mbwanji et al., 2024). Visual diagnosis of FGS by a trained expert is an important diagnostic tool, but there remain issues with specificity and the availability of equipment or trained healthcare workers. There is additionally no standardized clinical decision about FGS severity.

(b) Standardized protocols and requirements for data capture and sample processing.

Workshop participants highlighted that current R&D projects are often localized studies that lack standardized data capture, making comparisons and meta-analysis difficult. Data collection should be standardized, ensuring that diagnostic results, demographic data and clinical symptoms are recorded.

Correct collection, processing and storage of clinical samples are paramount to ensure good-quality diagnostic data are gathered. Standardizing sample collections across different studies so that the same preservative (e.g. ethanol/commercial) is utilized would be beneficial, as would the standardization of sample preparation or DNA extraction methods. Diagnostic evaluation studies to compare different Standard Operating Procedures (SOPs) would be beneficial, although labour intensive to perform. The GSA hosts a schistosomiasis resources database, which contains directories, bench aids, protocols and SOPs, as well as healthcare training guides for FGS. This database and these resources could be adapted for clinicians, midwives and community health workers.

For visual diagnostics

(1) Review existing diagnostic infrastructure and map out the availability of colposcopes within healthcare settings to tailor approaches to available resources.

There is very limited colposcope availability in FGS-endemic regions. Standard freestanding colposcopes are very expensive, and their use requires specialist training. Handheld colposcopes are more affordable and have been successfully trialled in research projects (Sturt et al., 2023), but availability outside the research setting remains limited (Søfteland et al., 2021). Given the importance of visual diagnosis for FGS, it is essential that access to the required equipment and training is achievable, especially in endemic, typically low-resource settings.

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(2) Update the WHO FGS pocket atlas and create open e-learning platforms that can guide colposcopy exams and capture images for further education/training.

As is the case for STIs, FGS diagnosis and severity cannot be conclusively determined using visual inspection or clinical history alone. In lieu of sufficient laboratory confirmation, a range of management protocols must be developed for different resource scenarios. Workshop participants commented that the WHO FGS pocket atlas, developed in 2015, contains too few images to capture FGS heterogeneity and ensure its accurate identification. Additionally, some potential manifestations of FGS (e.g. contact bleeding) are not formally defined as diagnostic criteria and, confusingly, may also be caused by the presence of STIs. Moreover, images taken during colposcopy are highly variable and need to be standardized in terms of image properties (e.g. magnification), and capture protocol (e.g. region of interest) to facilitate comparison and accurate FGS identification. The WHO FGS pocket atlas must be updated with a range of images for each of the clinical manifestations using high-quality colposcopy images and accompanied by a training module for the visual detection of FGS-associated lesions. This module should be hosted on an open e-learning platform, allowing nurses, midwives and community health workers to learn to diagnose FGS visually. Workshop participants discussed the possibility of using a smartphone app to make new, updated FGS atlas images more accessible (Martinez et al., 2024).

(3) Create a standardized virtual repository for colposcopy images to serve as an image bank for machine learning (ML) development and validation.

Computer-aided image analysis is already being explored for its potential to assist in the objective diagnosis of FGS (Holmen et al., 2015) but there is currently no centralized image database that can be used for ML development. Artificial intelligence (AI) is being trialled for cervical (pre-) cancer detection and a wide range of other medical fields; similarly, an ML-led algorithm for the detection of FGS lesions in images could help standardize FGS diagnosis and support healthcare professionals (Desai et al., 2022). Training an ML algorithm to correctly classify FGS requires many images that capture the region of interest (cervix), including examples with and without FGS-associated lesions. Such an algorithm would need to be able to recognize what is not FGS, particularly in the array of other diseases with visual manifestations on the cervix. This would require a large repository of images, accompanied by comprehensive laboratory and biopsy data. This computer-aided visual diagnostic tool would ideally be integrated into ML-led algorithms for other diseases such as STIs and CC and must be open source and not tied to a single imaging device to ensure access and adoption in low-resource settings.

For laboratory/field diagnostics

(1) Develop and clinically validate a molecular POC test to detect *Schistosoma* DNA from suitable samples.

Participants agreed that a sensitive and specific molecular test for the detection of *S. haematobium* DNA, suitable for use in a community healthcare setting, would contribute to the correct management of FGS. Multiple sampling types should be considered, including urine, serum, cervicovaginal swabs and menstrual blood. Genital self-sampling, a method shown to be highly acceptable for women, has demonstrated an increase in the number of PCR-based FGS diagnoses in a field setting (Rutty Phiri et al., 2020; Sturt et al., 2020b). A feasible POC test must consider ease of sample collection, ease of DNA extraction, suitability of the testing platform for use in the community (e.g. using portable isothermal platforms), affordability, ownership/responsibility for training, quality control and resource management (ensuring there is both a maintenance plan and a reagent budget). Additionally, synergy between FGS diagnosis and multiplex panels, including HPV and STIs, would be desirable. Molecular methods such as recombinase polymerase amplification and loop-mediated isothermal amplification have shown promise for detecting *Schistosoma* DNA from vaginal self-swabs (Archer et al., 2020, 2022; Van Bergen et al., 2024), but they remain to be scaled-up in low-resource settings. It was noted that although infrastructure for COVID-19 PCR-based testing now exists in most countries, access to and transport of the necessary consumables, and the need for trained expert users, make PCR implementation a continued challenge. An initial mapping exercise should be conducted to identify potentially suitable technologies that meet the REST-ASSURED criteria, an updated version of the REASSURED criteria that includes the rapid scale-up of diagnostic testing and transferability of assays, data and technology (Baldeh et al., 2024). This would help focus efforts and allow the development and clinical validation of a molecular POC test to detect *Schistosoma* DNA from suitable samples.

(2) Develop guidelines to improve the use of existing diagnostics for FGS.

Workshop participants discussed several key questions to define the purpose of a laboratory or POC diagnostic. For example, what added advantage does molecular diagnosis of FGS provide compared with established schistosomiasis diagnosis (e.g. urine microscopy or CAA detection) for screening and/or population-based mapping? How might these tools be applied in resource-poor settings versus in well-equipped travel clinics or reference diagnostic facilities? For the control of FGS, a more sensitive and specific diagnostic tool is required to aid the diagnosis of genital morbidity at an earlier stage, preventing the development of chronic lesions. However, the costs and availability of laboratory materials are prohibitive and have become a barrier. Therefore, affordable (but less sensitive) diagnostics will remain an important tool to guide healthcare professionals' decision-making. Guidelines should recommend which diagnostic tools should be deployed depending on the resource setting, the clinical presentation of the patient and users in different settings (e.g. researchers, health workers and clinicians).

Discussion

The purpose of the workshop, 'Female Genital Schistosomiasis: Translational Challenges and Opportunities', was to build on previous work from the BILGENSA network (Ndubani et al., 2024) by proposing solutions and actions that can be taken forward by the global health community to address identified FGS research priorities (Engels et al., 2020).

In the current workshop, discussions on community and capacity strengthening affirmed the widespread lack of awareness and routine training related to FGS. Participants recommended an integrated approach to make accessible materials available to health professionals (especially in endemic areas), community workers already involved in health promotion programmes, patients and their families, including men. To successfully raise awareness and

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educate the public about FGS, communications must be tailored towards different target groups who are involved in the cocreation and coordination.

Alongside efforts to raise community awareness, there must be capacity built into healthcare systems to ensure services are available to respond to increased numbers of women with FGS seeking medical advice. Workshop participants agreed that an important step to support this would be standardized data capture across SSA countries to estimate the disease burden and prevalence of FGS. This would provide essential data needed for health economic analyses that can be used to inform new policies on FGS prevention and control. Additionally, this would evaluate the affordability and cost-effectiveness of integrating FGS into existing SRHR or CC programmes.

The discussion on FGS therapeutics and novel targets highlighted that there is currently no consensus on the suitable endpoints to measure FGS treatment efficacy. Although there is agreement that PZQ is effective for preventing or killing adult *S. haematobium* worms, there is limited evidence of PZQ efficacy in resolving FGS lesions in the genital tract or reversing FGS-related health impacts such as subfertility or poor pregnancy outcomes. FGS clinical manifestations associated with different age groups may require different treatment regimens. A key action identified in this workshop was to create a working group, potentially under the umbrella of the WHO, to standardize FGS case definitions and clinically relevant outcomes and measures. These criteria can then be used to explore the effects of PZQ across different age groups in research evaluating existing and new treatments. This would ensure the timely distribution of PZQ to women and girls with FGS and those at risk of developing FGS. Concurrently, an evaluation of retrospective patient data from existing MDA programmes will help to identify how PZQ has impacted FGS prevalence and pathology.

Workshop participants highlighted several barriers to identifying new therapeutics, including a lack of novel targets, the absence of an FGS animal model and limited FGS-related biomarkers. A previously developed mouse model is not widely used due to the technical challenges of injecting eggs, and as it does not reproduce true disease, it is therefore not relevant to the current state of play (Richardson et al., 2014). Two important translational actions are therefore to conduct sufficiently powered, longitudinal studies of PZQ efficacy, including the assessment of novel targets, and studies to assess the efficacy of existing drugs for FGS treatment. In a discussion focused on drug repurposing, participants suggested several existing drugs that could be tested but emphasized the importance of conducting repurposing studies in real-world contexts where interactions with other medicines (such as for HIV and tuberculosis) can be fully evaluated.

In the sessions on diagnosis, it was agreed that no single visual or laboratory tool alone would be effective in the diagnosis of FGS, but that an algorithmic approach that combines different tools would be necessary. A key theme from these sessions was standardization – of reference tests and protocols for collecting, storing and processing diagnostic data and samples. Moreover, there is a need for more extensive open-access image datasets with clinical data that truly recapitulate all the diverse features of FGS and can be used to train clinical staff and ML models, with a view to using AI to support diagnosis. The BILGENSA network report highlighted the importance of decentralizing the diagnosis of FGS, including bringing diagnosis closer to the user (Ndubani et al., 2024). There was much discussion about the most appropriate technologies, including hand-held affordable colposcopes, home-based self-sampling (followed by PCR) and POC diagnostics by trained health professionals, and how to ensure these technologies are specific for FGS and amenable to use in low-resource settings. Several of the actions outlined here relate to this important research need, including mapping existing technologies, advancing new POC tools and developing guidance for the use of existing diagnostics.

Addressing the research needs in FGS requires strong political stakeholder engagement alongside global, regional and community effort and collaboration within governments, NGOs, research institutions and private healthcare systems, while not forgetting the endemic communities and patient groups affected. By identifying discrete actionable steps to move the field forward, it is hoped that this report will galvanize communities and collaborators around tangible research projects and pilots working towards specific shared endpoint objectives. Each of these endpoint objectives is essential for addressing the critical outstanding questions and barriers standing in the way of preventing, diagnosing and treating FGS.

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