

1 **Sensitive diagnostic tools and targeted drug administration strategies are needed to eliminate**  
 2 **schistosomiasis**

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36 **Abstract**

37 Although preventive chemotherapy has been instrumental in reducing schistosomiasis worldwide, serious  
38 challenges remain. These include the omission of certain groups from mass drug administration campaigns, the  
39 existence of persistent disease hotspots as well as the risk of recrudescence infections. Central to these challenges  
40 is the fact that the currently prescribed diagnostic tools to establish the burden of infection lack sensitivity,  
41 especially in low endemic settings, resulting in an underestimation of the true prevalence of active *Schistosoma*  
42 infections. This necessitates a re-evaluation and possible adaptation of current WHO-recommended control  
43 strategies. Recently, more targeted interventions and novel approaches have been employed, such as  
44 establishing infection burden by precision mapping to provide high resolution spatial information that delineates  
45 significant variations in schistosomiasis prevalence within a defined geographical area. Such information is  
46 instrumental in guiding targeted intervention campaigns. However, the need for highly accurate diagnostic tools  
47 in such strategies remains a crucial factor that is often neglected. The availability of highly sensitive diagnostic  
48 tests also opens up the possibility of applying sample pooling strategies, to reduce control programme costs. To  
49 achieve interruption of transmission and eventually elimination of schistosomiasis, better local targeting of  
50 preventive chemotherapy in combination with utilising more sensitive diagnostic tools is vital.

51

52 **Key-points**

53 \* Preventive chemotherapy has been key in reducing the burden of schistosomiasis but serious challenges  
54 remain

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56 \* Current diagnostic tools to detect *Schistosoma* infections as part of control programmes lack sensitivity

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58 \* Re-evaluation and adaptation of current WHO-recommended schistosomiasis control strategies is urgently  
59 needed

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61 \* The use of highly sensitive diagnostic tools is key in breaking the transmission cycle and moving towards  
62 sustained elimination of schistosomiasis

## 63 Introduction

64 Despite years of sustained control efforts, the global burden of schistosomiasis remains high with an estimated  
65 221 million people worldwide requiring preventive chemotherapy of which 90% resides in sub-Saharan Africa  
66 (1). This immense burden is exacerbated by the fact that schistosomiasis is strongly linked to poverty, limited  
67 access to potable water, and lack of adequate sanitation (2). Since 2001, the World Health Organisation (WHO)  
68 has strongly advocated for schistosomiasis morbidity control through preventive chemotherapy (World Health  
69 Assembly resolution 54.19 (3)) with a more recent expanded goal of elimination of schistosomiasis as a public  
70 health problem (World Health Assembly resolution 65.21 (4)).

71 While there have been successes in reducing the intensity of infections and associated morbidity through  
72 sustained mass drug administration (MDA) campaigns, schistosomiasis remains highly prevalent (5). In regions  
73 that have successfully reduced the intensity of infection to lower thresholds, the currently prescribed diagnostic  
74 tools are no longer reliable for control programmes treating these populations. Especially in areas with a low  
75 infection intensity these methods lack sensitivity and are therefore not able to accurately detect such low  
76 intensity infections and thereby underestimate the prevalence of active *Schistosoma* infections (6, 7). To break  
77 the cycle of transmission and shift towards sustained elimination of schistosomiasis, changes to the current  
78 global schistosomiasis control strategies are urgently needed (8, 9). The availability of more sensitive diagnostic  
79 tools presents opportunities to revisit these strategies in regions where a break in transmission may be feasible.

80 Strategic changes to advance the global control of schistosomiasis were discussed at an international workshop  
81 hosted by Leiden University Medical Center in the Netherlands in September 2017. The workshop brought  
82 together representatives from national control programmes, industry, donors and academia (research scientists,  
83 clinicians, and mathematical modellers) to develop a vision for sustained local interruption of transmission and  
84 the eventual successful elimination of schistosomiasis.

## 85 Challenges related to the current approach

86 The WHO's current strategy for controlling schistosomiasis focuses on reducing disease morbidity and  
87 transmission through periodic, targeted MDA with praziquantel (40 mg/kg body weight) administered to at-risk  
88 populations (10). As part of this strategy, the mean schistosomiasis prevalence is determined in an  
89 'implementation unit (IU)'; a geographical area where an MDA programme is being rolled-out. This IU can be a  
90 whole district or a sub-district (Figure 1A), for example an administrative, health or education district and it  
91 varies in size from country to country (11).

92 Usually, in 5-10 sentinel sites within such an IU a parasitological survey is performed to determine the overall  
93 prevalence in the entire IU (Figure 1B) (9, 12). The sentinel site can be a school with 50 children per school  
94 being surveyed. Based on the mean prevalence determined by the survey, the risk of schistosomiasis is  
95 categorised as low (<10%), moderate ( $\geq 10\%$  to <50%) or high ( $\geq 50\%$ ) for the whole IU (Figure 1C); a  
96 classification that defines the intervention strategy applied within this geographical area (13). Even though at  
97 sub-district level the burden of infection can be determined in more detail, this strategy does not sufficiently  
98 capture the focality of schistosomiasis, resulting in areas receiving over- or more importantly under-treatment  
99 (12).

100 Although initial implementation of the WHO MDA strategy has been successful in reducing morbidity (14-16)  
101 there are several opportunities for optimisation. MDA strategies traditionally target school-age children, a group  
102 within which the prevalence of schistosomiasis is often higher compared to other groups and which can be  
103 conveniently reached by programmes at one location (a school). However, this strategy fails to cover other  
104 groups that are at high risk of schistosome infection, for example preschool-age children and adults exposed to  
105 infested water through their occupations (e.g. fishermen, farmers, women doing laundry and irrigation workers)  
106 (17, 18). As such, these groups remain potential active reservoirs for continued transmission in a community.  
107 Preschool-age children are excluded due to safety concerns and poor adherence to praziquantel, although this  
108 concern is likely to be addressed with the development of a paediatric formulation for praziquantel (19).  
109 Likewise, WHO guidelines recommend the inclusion of pregnant and lactating women in MDA campaigns, but  
110 these groups often remain excluded also due to safety concerns despite the growing body of evidence  
111 demonstrating efficacy and safety of praziquantel for their treatment (20, 21). Exclusion of certain groups  
112 becomes a critical issue if the goal is community-wide control and elimination of schistosomiasis.

113 The commitment of Merck to support the WHO through the donation of praziquantel for preventive  
114 chemotherapy in school-aged children in Sub-Saharan Africa (22) has been pivotal to schistosomiasis control  
115 efforts. However, with the scale-up of MDA programmes, many African countries have been faced with the  
116 challenge of bridging the gap between the demand for praziquantel and what is available via the donation  
117 programme (23). Moreover, the currently recommended MDA dosage for praziquantel may be leading to  
118 suboptimal cure rates and prolonged low intensity infections within some communities. These consequences  
119 will be even more substantial and pronounced when percentages of population coverage of MDA will be  
120 reduced, leaving larger numbers of infected people untreated.

121 Additionally, in certain areas control of schistosomiasis is hampered by the existence of ‘persistent hotspots’;  
122 geographical regions where MDA programmes have been in operation for several years, yet remain unable to  
123 achieve the forecasted declines in prevalence or intensity of schistosomiasis (24-27). Persistent hotspots have  
124 been identified across Africa including Kenya (28), Mali (29, 30), Sudan (31) and Tanzania (24, 32). These  
125 hotspots likely require approaches that combine MDA with multi-sectoral efforts such as health education,  
126 improvements to sanitation and potable water supply, environmental and vector control as well as future use of  
127 vaccines (33-37).

128 Another challenge in the control of schistosomiasis exists in parts of Asia where the prevalent schistosome  
129 species (*S. japonicum*, *S. mekongi* and *S. malayensis*) are known to be zoonotic and have several animal  
130 definitive hosts as a reservoir of infection (38). Also in African schistosomiasis, animal reservoirs have been  
131 described (39, 40). In such areas, the control and elimination of schistosomiasis is even more problematic since  
132 the management of animal reservoirs is imperative (38). In addition, molecular studies have also found evidence  
133 of genetic interactions between human and animal schistosomes within the African continent and the emergence  
134 of hybrid species indicative of some zoonotic spill-over (41, 42).

135 Classic diagnosis of schistosomiasis as part of control programmes is often still based on parasitological  
136 assessment of urine or stool, depending on the schistosome species endemic in the area. These diagnostic  
137 methods are known to lack sensitivity in detecting infections of low intensity, resulting in an underestimation of  
138 the burden of infection (7). Identifying areas with low infection intensities using accurate diagnostic tools  
139 combined with cost-effective strategies for implementation is essential for achieving elimination of  
140 schistosomiasis. This is also important for dealing with ‘subtle morbidities’ that could have long-term impact on  
141 the quality of life of individuals including effects on cognitive development (43). Control programmes struggle  
142 with how to tackle low prevalence settings where the factors sustaining transmission at lower levels are poorly  
143 understood and interruption of transmission has not yet been achieved (9, 33, 34). In addition, low endemic  
144 areas likely require continuous surveillance with highly sensitive diagnostic tools, as the risk of prematurely  
145 stopping MDA might very well result in infection levels returning to pre-MDA levels shortly after cessation of  
146 MDA (recrudescence infections) (37, 44). As for persistent hotspots, an integrated control approach is likely  
147 required to achieve these epidemiological targets.

#### 148 **Importance of precision mapping and more targeted interventions**

149 Locating exactly where active transmission occurs and which individuals within a community still harbour  
150 living worm pairs, is particularly relevant as schistosomiasis is heterogeneously distributed, meaning that an  
151 endemic region can be considered as a collection of (micro)foci (45). There is a lack of clear guidelines that  
152 account for the potential effects of this natural heterogeneity, or focality, on programme design. Recent studies  
153 by the Schistosomiasis Consortium for Operational Research and Evaluation (SCORE) have shown a large  
154 variability in MDA efficacy at the community level (24, 28). Therefore, existing control guidelines need to be  
155 adapted with greater focus on geographical areas of low endemicity that are likely to achieve transmission  
156 interruption. In these areas, sampling grids can be narrowed by increasing the number of sites being sampled; a  
157 concept that has been termed ‘precision mapping’ (12). In order to demonstrate the precision mapping approach  
158 in Cameroon, Tchuem Tchuenté *et al* exhaustively sampled all schools in two schistosomiasis-endemic districts  
159 representing geographical areas characterised as being low and high with respect to schistosomiasis transmission  
160 (12). This approach produced high-resolution mapping information that showed significant variations in  
161 schistosomiasis prevalence between districts and sub-districts (called implementation units, IU), which would  
162 not have been detected with conventional mapping approaches that are part of the current global control  
163 strategies. Analysis of data from precision mapping can be used to guide targeted and intensified interventions  
164 in high-risk areas, providing a cost-efficient and judicious use of donated praziquantel. Furthermore, this  
165 approach presents an opportunity to zoom in on an IU to identify areas of significant transmission and the

166 advantage to specifically target the identification of individuals living in a low-endemic community who  
167 harbour significant intensities of living adult worms (the so called ‘super-spreaders’ (46)).

### 168 **Importance of highly sensitive diagnostics**

169 The success of any strategy to tackle schistosomiasis hinges on the ability to obtain an accurate picture of the  
170 burden of infection in a given community, as ‘improvement can only come from accurate measurement’ (Lord  
171 Kelvin, 1883) (47). The necessity of accurate diagnostic tools with high sensitivity in these strategies is often  
172 neglected. To achieve the goal of elimination of schistosomiasis, highly sensitive and specific diagnostic tools,  
173 that ideally are field-applicable, are needed to monitor the burden of infection.

174 Several diagnostic tools have demonstrated to be useful alternatives compared to conventional diagnostic  
175 methods currently used by national control programmes, such as the widely used field-applicable point-of-care  
176 circulating cathodic antigen (POC-CCA) test (48, 49). Even though this test has been recommended as a  
177 replacement for traditional microscopy (50), it is limited to the detection of intestinal schistosomiasis and still  
178 lacks sensitivity in detecting infections of low intensity (51, 52). A more promising alternative is the highly  
179 sensitive and specific laboratory-based up-converting phosphor lateral flow (UCP-LF) test that detects  
180 *Schistosoma* circulating anodic antigen (CAA) (53-56). It is a genus-specific test which detects all *Schistosoma*  
181 species in blood and urine samples, and may potentially be able to detect a single worm pair by increasing  
182 sample volume (56, 57). Furthermore, the UCP-LF CAA test is amenable to pooled sample testing strategies  
183 (58). Individuals whose pooled urine samples are found negative by the UCP-LF CAA test can be assumed to all  
184 be free of schistosome worms, or at least below a set threshold in worm load, while in CAA-positive urine  
185 pools, one or more individuals harbour a worm burden which might be relevant for further transmission.  
186 Individual urine samples can then be subsequently tested to identify infected individuals within a positive  
187 sample pool, in order to only treat infected individuals and thereby save drugs. Compared to more exhaustive  
188 sampling approaches, such pooling strategies can potentially reduce control programme costs (59). Although the  
189 UCP-LF CAA test is still lab-based, steps are underway to develop a more field-applicable version of this test  
190 (55, 58, 60). Clearly, a reliable and easy-to-use rapid diagnostic test is a prerequisite for the development of test-  
191 and-treat strategies, with or without pooled sampling, as well as to facilitate the clinical diagnosis of  
192 schistosomiasis at point-of-care settings and the targeted use of praziquantel.

193 Other more sensitive and specific diagnostics methods include polymerase chain reaction (PCR)-based methods  
194 for the detection of schistosome-specific DNA in clinical samples (urine, faeces or blood) (7, 61). One approach  
195 that has been designed for field use is loop-mediated isothermal amplification (LAMP), an advanced DNA-  
196 based detection method that amplifies DNA without a thermocycler and in some instances, can have higher  
197 sensitivity compared to conventional PCR (62-64). Another potentially field-applicable technique is isothermal  
198 recombinase polymerase amplification (RPA) for schistosome-specific DNA detection applicable to both *S.*  
199 *haematobium* (65) and *S. mansoni* (66).

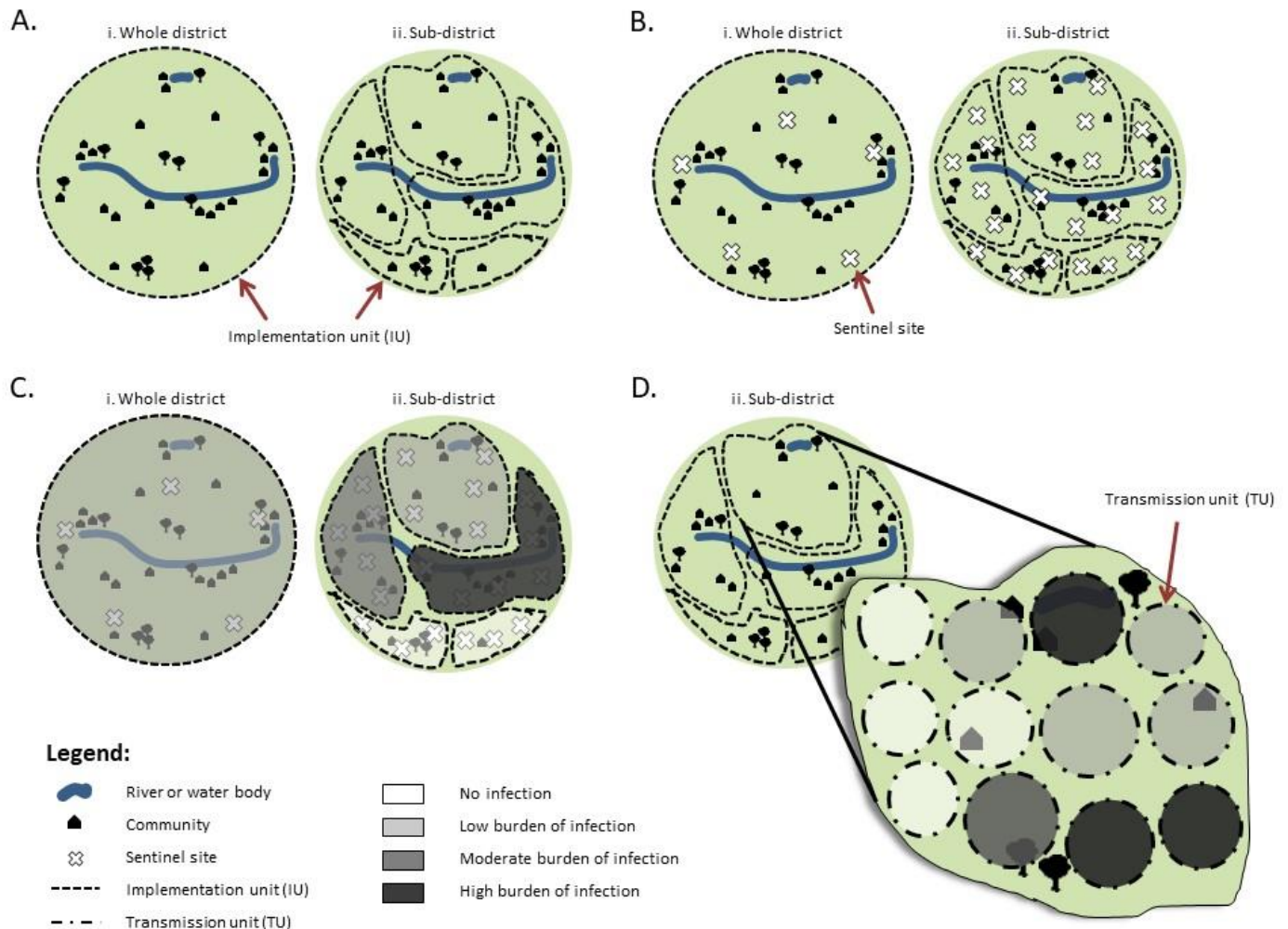
### 200 **Integrating sensitive diagnostics into an intensified focal test-and-treat strategy**

201 In a theoretical schistosomiasis endemic area, comprised of one or more IUs, where the prevalence of infection  
202 has been determined to be low by standard parasitological methods (i.e. less than 10% overall prevalence and  
203 less than 1% prevalence of heavy infections), an intensified focal test-and-treat strategy, using highly accurate  
204 diagnostic tools, should at least be included to shift transmission dynamics within these geographical areas  
205 towards a break in transmission.

206 When applying the precision mapping approach in such an area, the burden of infection within an IU should be  
207 estimated from a larger number of sentinel sites, rather than a sampling from 5-10 sites as is conventionally  
208 recommended. This increased sampling from a larger number of sentinel sites would require pooling multiple  
209 samples in order to reduce the total number of tests needed as a cost-saving measure (58, 59). Given the focal  
210 nature of schistosomiasis, sampling designs should also consider proximity to water contact points where  
211 transmission is suspected.

212 In one scenario discussed at the workshop, an IU at sub-district level can be divided into separate ‘transmission  
213 units’ (TU, Figure 1D); a proposed geographical area limited to one or few transmission sites. So, instead of the  
214 current strategy in which 5-10 sentinel sites within an IU are being sampled, the whole IU is divided into  
215 smaller TUs. By integrating a pooling strategy using a highly sensitive diagnostic test, a whole TU will be

216 sampled and tested, leading to a quantitative evaluation of the overall infection burden within each TU.  
 217 Mathematical modelling could provide valuable information on the best pooling strategy, taking into  
 218 consideration age-groups or risk groups, as well as expected infection levels based on pre-control endemicity  
 219 and history of control, to determine optimal pool size (58, 59). Information from existing databases on  
 220 correlation between different diagnostic tests could also be used to develop a predictive model to estimate for  
 221 example CAA or DNA loads and linking these individual measurements to transmission potential within a given  
 222 area. The outcome of testing pooled samples with a highly sensitive diagnostic test in combination with the  
 223 predictions of the model(s) would then guide the prevalence thresholds that should be set to determine the  
 224 appropriate control strategy that will be embarked on within each TU.



225

226 **Figure 1. Schematic representation illustrating the current strategy of sampling within an intervention**  
 227 **unit in comparison to a mapping approach at a smaller level based on a pooled sampling strategy.**  
 228 Currently, according to the WHO, areas are divided into implementation units (IU) (A) which can vary in size;  
 229 for example a whole district (A-i) or a sub-district (A-ii). The burden of infection in each IU is determined and  
 230 monitored by sampling from 5-10 sentinel sites (B) using conventional parasitological diagnostic tools. The  
 231 burden of infection is then categorised as low, moderate or high for each IU (C). By further dividing sub-district  
 232 IUs into smaller transmission units (TU) (D), and instead of sampling from 5-10 sentinel sites applying a  
 233 pooling strategy to the whole TU, a bigger area will be sampled from. This results in more accurate data for  
 234 mapping and quantifying the distribution of schistosomiasis as well as to identify communities at risk.

235 **Table 1: Proposed treatment strategy based on infection burden**

<b>Infection burden established by sampling</b>	<b>Recommended treatment strategy*</b>
I. High infection burden	Intense MDA (annual or biannual treatment of all high-risk groups as well as community-wide treatment)
II. Medium infection burden	Regular MDA (annual community-wide treatment)
III. Low infection burden (near elimination)	Intensified focal test-and-treat (multiple rounds per year) and frequent surveillance, using the most sensitive diagnostic tool available in combination with pooled sampling
IV. No infection (anymore)	No MDA, regular surveillance, using the most sensitive diagnostic tool available in combination with pooled sampling

236 \* Combined with integrated intervention measures, see text

237 From the strategy outlined above, we envisage four scenarios that may reflect the burden of infection from  
 238 surveying each TU (shown in Table 1). The corresponding recommended strategy should then also be  
 239 implemented at TU level. In TUs found to have a high infection burden, for instance potential ‘hotspots’ or  
 240 ‘persistent hotspots’, intense MDA of yearly or twice-yearly treatment should be rolled out following existing  
 241 control strategies. Additional samples should be taken not only from school-age children, but also from high-  
 242 risk groups (such as fishermen, car-washers, women doing laundry, etc.) and testing stratified according to these  
 243 groups. The strategy could be adapted to treatment for each positive group in addition to all school-age children;  
 244 and the entire group could be monitored and followed up over a two-year period. For TUs where a medium  
 245 infection burden is established, a regular MDA programme of yearly community-wide treatment should be  
 246 implemented. In areas where the burden of infection is found to be low, an intensified test-and-treat strategy  
 247 with multiple rounds of testing and treating per year should be implemented after identifying the high-risk  
 248 groups within each community. In addition, the identification, treatment and monitoring of individuals who still  
 249 harbour high worm infections also needs to be taken into account in this strategy. Furthermore, knowledge  
 250 about local transmission sites with respect to aquatic biology and social behaviour patterns is indispensable in  
 251 tackling and reducing exposure. Individual worm levels could also be included to guide local or regional  
 252 interventions. In TUs found to be negative, no MDA would be carried out but groups should be followed-up and  
 253 tested over a given period of time using a cost-efficient sample pooling strategy. It would be important to know  
 254 if these areas have always been negative or are negative after prolonged control since the monitoring approach  
 255 depends on the potential for transmission in the area (best reflected by the pre-control endemicity). Obviously,  
 256 all strategies also need to include other integrated multisectoral approaches such as health education, snail  
 257 control, and water, sanitation and hygiene (WASH) initiatives. Classic xenomonitoring augmented with DNA  
 258 methods that can identify infected snail hosts is especially important to determine environmental risk accurately  
 259 (67), as well as monitoring of schistosome infection in locations where zoonotic spill-over may occur. Further  
 260 innovations such analysis of water for environmental DNA (eDNA) (68), signatures of schistosomes with taxon  
 261 specific probes, could be very powerful to verify putative interruptions of transmission.

262 At the national level, a surveillance response mechanism would need to monitor these focal test-and-treat  
 263 strategies. This includes modelling for prediction and guiding the intervention, monitoring of infection and  
 264 mechanisms to evaluate interventions (69). Global positioning system (GPS) mapping could be used to  
 265 determine precise locations of infected people of all ages and their households (70). However, privacy issues  
 266 need to be taken into consideration. Innovations such as surveying snail environmental DNA (eDNA) in water  
 267 bodies (68, 71) are additional tools that can be used to monitor transmission. Lessons can also be learnt from the  
 268 Global Polio Eradication Initiative which uses environmental surveillance of poliovirus in sewage to monitor  
 269 the virus (72).

270 After presumed interruption of transmission has been achieved, communities should still, ideally, be monitored  
 271 longitudinally using highly sensitive and specific assays using the UCP-LF CAA test and eventually also  
 272 serology. After a number of years with no new infections being detected, new-borns and young children would  
 273 have to be followed to assess their exposure to schistosomes (44, 73), which could be done through for example  
 274 targeted anti-schistosomal antibody testing (74, 75). In addition, the movement of individuals from regions that  
 275 are still endemic for schistosomiasis into post-transmission areas would have to be monitored, and infected  
 276 individuals promptly treated. The development of commercially available highly sensitive tests would be  
 277 indispensable in targeting these groups in this post-transmission phase.

278 Given that current schistosomiasis control programmes in sub-Saharan Africa rely heavily on donated  
279 praziquantel for MDA campaigns, the proposed test-and-treat strategy will enhance cost-efficiency. The  
280 availability of a paediatric praziquantel formulation for young children will further support and strengthen a  
281 community-wide targeted treatment approach.

282 The successful implementation and efficient rollout of the proposed strategy would hinge on close cooperation  
283 between key international players (such as WHO) and stakeholders within endemic countries. Within these  
284 countries, engagement with national and local authorities would guarantee local ownership and responsibility  
285 for the strategy and its implementation. Targeted implementation at more local levels such as a TU could be  
286 more complex due to logistical challenges and the lack of adequate structures. Therefore, strengthening overall  
287 neglected tropical disease (NTD) coordination structures at national and sub-national levels, including the  
288 building of local capacity, would assure the proper execution of the proposed strategy, as well as effective long-  
289 term monitoring, evaluation and overall sustainability.

290 Additionally, it would be essential that endemic countries adopt and incorporate the strategy into the  
291 development of their NTD master plans. This would be achieved through local and international stakeholders  
292 working closely with endemic country NTD expert committees that are responsible for coordinating the  
293 direction of national NTD goals and policies (including for schistosomiasis) and ensuring that these are in line  
294 with regional and global targets. Combining all these efforts is essential for improved focal targeting of  
295 preventive chemotherapy in combination with more sensitive diagnostic tools in order to achieve interruption of  
296 transmission and the eventual elimination of schistosomiasis.



297 **Conclusion**

298 The persistent global burden of schistosomiasis despite continuous large-scale MDA, requires a rethinking and  
299 revision of both intervention strategies and the diagnostic tools that enable these strategies. Especially in areas  
300 of low infection intensity, non-invasive pooled sample testing with highly accurate diagnostic tools should be  
301 implemented by national control programmes in adapted control strategies that ensure cost-efficiency in  
302 monitoring and evaluation, as well as longer-term surveillance. We believe this will be the way to go to achieve  
303 interruption of transmission and eventually elimination of schistosomiasis.

304

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319

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