

1           **A call to strengthen the global strategy for schistosomiasis and**  
2           **soil-transmitted helminthiasis: the time is now**

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39           **Summary Word Count: 221**

40           **Main Text Word Count: 2,127**

41           **Tables and Figures: 1 panel, 1 table**

42           **References: 49**

43

44 **Keywords:** neglected tropical diseases, schistosomiasis, soil-transmitted helminthiasis, mass  
45 drug administration, preventive chemotherapy, guidelines, health policy

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53 **Summary**

54 In 2001, the World Health Assembly (WHA) passed the landmark WHA 54.19 resolution for  
55 global scale up of mass administration of anthelmintic drugs for morbidity control of  
56 schistosomiasis and soil-transmitted helminthiasis (STH), which affect over 1.5 billion of the  
57 world’s poorest people. Since then, over a decade of research and experience has yielded critical  
58 new knowledge on the control and elimination of these helminthiases. However, the global  
59 strategy has remained largely unchanged since the original 2001 WHA resolution and associated  
60 World Health Organization (WHO) guidelines on preventive chemotherapy. Here, we highlight  
61 recent advances that, taken together, support a call to revise the global strategy and guidelines for  
62 preventive chemotherapy and complementary interventions against schistosomiasis and STH.  
63 This includes the development of guidance that is specific to goals of “morbidity control” and  
64 “elimination of transmission.” We quantify the result of forgoing this opportunity by computing  
65 the yearly disease burden, mortality, and lost economic productivity associated with maintaining  
66 status quo. Without change, we estimate that the population of sub-Saharan Africa will likely  
67 lose 2.3 million disability-adjusted life years and US\$3.5 billion of economic productivity every  
68 year, which is comparable to recent acute epidemics, including the 2014 Ebola and 2015 Zika  
69 epidemics. We propose that the time is now to strengthen the global strategy to address the  
70 substantial disease burden of schistosomiasis and STH.

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## 76 **Personal View**

### 77 Introduction

78 Over 15 years ago, the World Health Assembly (WHA) passed the landmark WHA 54.19  
79 resolution to address the 1.5 billion people affected by schistosomiasis and soil-transmitted  
80 helminthiasis (STH; including ascariasis, hookworm disease, and trichuriasis).<sup>1,2</sup> The WHO  
81 subsequently created a Department of Neglected Tropical Diseases (NTDs), and produced  
82 guidelines that set a new paradigm for a public health approach against many NTDs, including  
83 schistosomiasis and STH, through a strategy of preventive chemotherapy (via ‘mass drug  
84 administration’).<sup>3</sup> This strategy involves large-scale, periodic (e.g., yearly) empiric treatment of  
85 entire populations and typically focuses on groups assumed to have the greatest disease  
86 morbidity, such as school-aged children (ages 5-15 years) for schistosomiasis and pre-school and  
87 school-aged children (ages 1-15 years) for STH.<sup>3,4</sup> These helminthiasis are characterized by  
88 mostly chronic, often insidious helminth-specific sequelae ranging from mild to severe  
89 morbidities. These include anaemia, chronic abdominal pain, and malnutrition, and also more  
90 rare and serious complications including bladder cancer, hepatosplenomegaly, and death for  
91 schistosomiasis and small bowel obstruction and rectal prolapse for STH.

92 Today, under the auspices of the WHO Department of NTDs, catalyzed by the 2012  
93 London Declaration for NTDs, and with large-scale support from governments, pharmaceutical  
94 companies, and NGOs, preventive chemotherapy programmes have achieved impressive gains.  
95 In 2015 alone, these programmes delivered treatment to 65 million people using praziquantel  
96 (against schistosomiasis) and 565 million people using albendazole or mebendazole (against  
97 STH) throughout Africa, Asia, Latin America, and the Middle East.<sup>5,6</sup> Over this period, there  
98 have been corresponding reductions in the number of infections and global disease burden

99 estimates.<sup>1,2,7</sup> This strategy of “morbidity control” has defined a goal of “eliminating helminths  
100 as a public health problem.” For STH, this is defined as <1% moderate-to-heavy intensity  
101 infection prevalence in at risk populations, as determined by egg counts on microscopic  
102 examination, and for schistosomiasis, the goal has been expressed as <1% heavy-intensity  
103 infections based on egg counts in stools or urine.

104 While this commendable morbidity control strategy has certainly led to success, mainly  
105 by averting long-term sequelae in school-aged children, the reinfection rate has been high in  
106 most settings.<sup>8,9</sup> Unfortunately, even countries that have successfully implemented the  
107 recommended preventive chemotherapy strategy for schistosomiasis and STH—i.e., repeated  
108 treatment of school-aged children at WHO-recommended  $\geq 75\%$  coverage—have met challenges  
109 in achieving optimal morbidity control or the more ambitious goal of transmission  
110 elimination.<sup>8,10,11</sup> This finding is consistent with estimates by the Global Burden of Disease  
111 (GBD) study and others that have documented how progress has lagged behind for  
112 schistosomiasis and STH relative to many other NTDs.<sup>12</sup> To address this challenge, in light of  
113 the past decade of data and experience from the field, we re-visit the global strategy for  
114 preventive chemotherapy and complementary interventions against schistosomiasis and STH.

#### 115 Preventive chemotherapy

116 As the post-2020 agenda for NTDs is considered, there is growing interest in improving the  
117 morbidity control strategy, and when appropriate, shifting towards a more ambitious goal of  
118 “elimination of transmission,” which is defined as interruption of transmission. The critical,  
119 policy-relevant question to be asked is how we can leverage new evidence to strengthen current  
120 strategies and guidelines for preventive chemotherapy to achieve these goals (see Panel 1). The  
121 current strategy of morbidity control emphasises treatment of school-aged children alone (with

122 extension to preschool-aged children for STH); however, adolescents and adults (15 years and  
123 older; including pregnant women) and younger children (<5 years) in the case of schistosomiasis,  
124 are often infected and are not rigorously addressed in the current global strategy or in  
125 parasitological monitoring.<sup>3,4,13</sup> If left untreated, these groups can serve as a “hidden reservoir”  
126 and potential source of reinfection for all age groups. Modelling studies indicate that expanding  
127 treatment from school-aged children alone to entire communities could substantially reduce  
128 reinfection across all age groups, and avert accumulated morbidity in these populations,  
129 especially schistosomiasis-related chronic sequelae in preschool-aged children.<sup>10,13-16</sup> The  
130 relative advantage of community-based treatment has been further supported by a recent  
131 systematic review and meta-analysis of observational studies.<sup>17</sup> Furthermore, expanded  
132 community-wide treatment can be highly cost-effective because of this averted morbidity, even  
133 if transmission is not eliminated.<sup>10,18</sup> To achieve community-wide coverage, countries could  
134 utilize distribution networks from other community-based health platforms for feasibility and  
135 cost-efficiency, including integration with vaccination programmes, Demographic and Health  
136 Surveys (DHS), or through continued use of lymphatic filariasis or onchocerciasis drug  
137 distributors who have delivered community-wide anthelmintics (e.g., ivermectin, albendazole)  
138 at scale.<sup>19,20</sup>

139 Guidelines currently provide “prevalence thresholds”, above which a preventive  
140 chemotherapy strategy is recommended, but given recent experience these may be too restrictive  
141 to achieve optimal averted disability and cost-effectiveness even under a goal of morbidity  
142 control. These prevalence thresholds are based on expert opinion and a historically more limited  
143 drug supply, and have remained largely unchanged for over a decade.<sup>3,4</sup> While these thresholds  
144 have guided efforts in preventive chemotherapy, analysis of new data suggest they can be

145 improved by considering transmission dynamics and health economics.<sup>10,18</sup> Notably, a recent  
146 study that rigorously assessed these prevalence thresholds found them to often be too restrictive  
147 on the basis of morbidity control (measured in disability-adjusted life years (DALYs)) and cost-  
148 effectiveness, especially for schistosomiasis.<sup>18</sup> For example, annual school-based treatment of  
149 schistosomiasis was cost-effective at 5% prevalence rather than the currently recommended 50%  
150 prevalence, and new prevalence thresholds were defined for community-wide coverage for both  
151 sets of helminthiases.<sup>18</sup> Importantly, while expanded treatment would have great potential to  
152 avert disease morbidity, reduce overall reinfection, and prevent chronic sequelae in young  
153 children, the potential emergence of drug resistance from increased treatment pressure is a  
154 concern. Therefore, rigorous methods to monitor drug efficacy will be essential, although  
155 community-wide treatment at 75% coverage still falls under the best practices according to  
156 conservative estimates from veterinary literature.<sup>21</sup> This concern can further be addressed by a  
157 longer-term but necessary research and development agenda to create improved drug regimens  
158 with greater efficacies against schistosomiasis and STH (particularly trichuriasis), where drug  
159 efficacy may be lower than expected, or even anthelmintic vaccines to prevent reinfection.<sup>22-24</sup>  
160 New diagnostics for helminths (e.g., point-of-care circulating cathodic antigen urine cassette test  
161 for *Schistosoma mansoni*) can also be applied to guide new treatment thresholds.<sup>25</sup>

162 Re-examination of the preventive chemotherapy strategy should also consider recent  
163 evidence from the Cochrane Collaboration and Campbell Collaboration systematic reviews and  
164 meta-analyses of trial data that suggests limited benefit of school-based preventive chemotherapy  
165 for STH, although should be considered within the limitations of the data and substantial debate  
166 surrounding potential methodological challenges (see Appendix).<sup>26-30</sup> For example, studies may  
167 be underpowered to detect a meaningful effect and relevant health outcomes may not be realized

168 within the short timeframe of most trials. Furthermore, children may have high rates of  
169 reinfection in school-based programmes that limits improvements to health, but this could be  
170 overcome with community-wide treatment strategies.<sup>10,16,17</sup>

171 The updated global strategy for preventive chemotherapy should increase attention to  
172 country-level coordination of integrated programmatic delivery (i.e., giving multiple medicines  
173 in the same programme) that would yield substantial cost-savings and biological synergies within  
174 the constraints of proven feasibility.<sup>10,18,31,32</sup> While integrated preventive chemotherapy  
175 guidelines do exist, improving country-level coordination of these programmes would benefit  
176 cost-efficiency.<sup>18,33</sup> The prevalence threshold itself is lower for adding another medicine in  
177 addition to an existing treatment programme compared to a standalone programme due to  
178 reduced delivery cost, and since the majority of cost is from delivery and not the drugs  
179 themselves.<sup>10,31</sup> For example, programmatic delivery of praziquantel should include albendazole  
180 or mebendazole, as done by the Schistosomiasis Control Initiative, since STH is most often co-  
181 endemic and co-administration is safe.<sup>32</sup> The integration of these programmes should work  
182 within the constraints of the drug supply and the relevant ecological zone (e.g., national, sub-  
183 national, community) that addresses the focal nature of schistosomiasis, which is in contrast with  
184 the more homogenous nature of STH.

#### 185 Complementary interventions

186 The global strategy should include water, sanitation, and hygiene (WASH) interventions,  
187 information, education, and communication (IEC) programmes, and focal snail control (for  
188 schistosomiasis), especially when elimination of transmission is the goal. Coordinated guidelines  
189 are needed that define the conditions (e.g., prevalence threshold, programmatic goals) where  
190 each complementary intervention should be implemented alongside preventive chemotherapy



191 within the broad framework of local health needs. While WASH programming, IEC, and snail  
192 control are not the focus of current global efforts, growing evidence supports the need for greater  
193 inclusion within the updated strategy, especially where disease dynamics are recalcitrant to  
194 preventive chemotherapy alone or elimination of transmission is the goal.

195 The implementation of the WHO WASH-NTD global strategy will likely be essential to  
196 eliminate transmission.<sup>34</sup> Observational studies have provided evidence for the relationship  
197 between various components of WASH (including improved water, sanitation, and hygiene and  
198 health behavior) and helminth prevalence and mean intensity.<sup>35-39</sup> However, the experimental  
199 evidence from trials is mixed, and studies are ongoing to validate the data from observational  
200 studies.<sup>37,39,42</sup> Regardless, these programmes are likely to have substantial spillover benefit by  
201 reducing the incidence of other infectious diseases improving country-level cost-effectiveness.<sup>39</sup>

202 The importance of snail control in schistosomiasis control and elimination has been  
203 supported by a recent meta-analysis, empirical analyses of historical data and modelling  
204 studies.<sup>15,43,44</sup> The inclusion of multiple means of snail control within a coordinated strategy  
205 alongside preventive chemotherapy for schistosomiasis is an important step forward in  
206 eliminating transmission in low endemicity settings and also controlling disease morbidity in  
207 high endemicity settings.

#### 208 Guidelines for morbidity control versus elimination of transmission

209 Distinct programmatic guidance is urgently needed that is specific to the different goals of  
210 “morbidity control” or “elimination of transmission,” and is informed by the setting’s local  
211 helminthiasis epidemiology and health priorities of the country. The decision on strategy should  
212 further be made on a sub-national basis with consideration of the focal nature of schistosomiasis.  
213 Importantly, disease burden differs considerably among settings, and elimination of transmission

214 may not be possible in all locations with existing tools and resources. High-burden settings may  
215 set a near-term goal of morbidity control, while low-burden settings may target elimination of  
216 transmission. In all cases, settings should first aim to achieve effective morbidity control before  
217 expanding to a goal of elimination of transmission.

218 To achieve this, settings targeting STH for morbidity control should focus on ensuring high  
219 drug coverage in all risk groups, including preschool-aged children and adults. In contrast,  
220 settings with low prevalence may set a goal of eliminating transmission and may prioritise non-  
221 drug interventions such as WASH programming, snail control, and intensive surveillance.<sup>45</sup> In all  
222 cases, the country's goals and resource constraints will inform this choice, and distinct strategic  
223 recommendations should be available to reflect these different scenarios. Importantly,  
224 programmatic goals should be established with full country ownership of these programmes,  
225 especially in regions with an improving economy and health systems. In developed countries,  
226 particular attention should be given to “blue marble health” which recognises the sizable  
227 proportion of the global burden of helminthiasis that occurs in the poorer populations of wealthy  
228 countries will require distinct strategies and political support structures.<sup>46</sup>

229 The proposed revision to the global strategy may substantially expand the target population  
230 for preventive chemotherapy and resources needed for complementary interventions. In countries  
231 that have yet to achieve the 2020 goal of at least 75% drug coverage of all at-risk populations,  
232 the development of an updated strategy will serve to clarify resource, drug supply, and  
233 programmatic needs to attain the 2020 goal and beyond. In settings that have reached 75% drug  
234 coverage targets, strengthened guidance should provide an evidence-based strategy towards a  
235 more ambitious and well-defined goal of optimal morbidity control or elimination of  
236 transmission without allowing for infection rebound.

237 The historic creation of many aspirational targets in global health, including the “3 by 5”  
238 initiative for HIV/AIDS, the Millennium Development Goals (MDGs), and the London  
239 Declaration on NTDs illustrates the potential of setting a higher bar to improve human health.  
240 The inclusion of NTDs as a specific target within the UN Sustainable Development Goals  
241 (SDGs) signifies the role in achieving Universal Health Coverage.<sup>47</sup>

242 To quantify the potential gains of strengthening the global strategy for schistosomiasis and  
243 STH, we compare recent evidence-based strategies for preventive chemotherapy relative to the  
244 current global strategy and idealized WHO guidelines. Without change, we estimate that the  
245 population of sub-Saharan Africa will likely lose 2.3 million DALYs and US\$ 3.5 billion of  
246 economic productivity every year, which is comparable to the impact of recent acute epidemics,  
247 including the 2014 Ebola and 2015 Zika epidemics combined (see Table 1, Appendix).

#### 248 Conclusions

249 With a shared goal of reducing the burden of NTDs on the world’s poorest people, and  
250 following the leadership of WHO Director-General Dr. Margaret Chan and colleagues around  
251 the world in NTDs, we respectfully advocate for revision of the global strategy and associated  
252 WHO guidelines for schistosomiasis and STH to incorporate new knowledge and experience  
253 gained over the last 15 years. If we miss this opportunity, then we fail to do all we can to help the  
254 populations who suffer the greatest burden of helminthiases and other NTDs.

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397 **Panel and Tables**398 **Panel 1: Key steps for strengthening the global strategy for schistosomiasis and STH**

Key step	Strength of evidence
<b>Step 1: Update strategy for preventive chemotherapy</b>	
<ul style="list-style-type: none"> <li>Expanded treatment across broader age groups (i.e., community-wide treatment)</li> </ul>	Modelling and cost-effectiveness studies <sup>10,14,18,48</sup> with support from systematic review and meta-analysis of observational studies <sup>17</sup>
<ul style="list-style-type: none"> <li>Lower prevalence thresholds for treatment, especially for schistosomiasis</li> </ul>	Modelling and cost-effectiveness studies <sup>18</sup> with support from observational studies
<ul style="list-style-type: none"> <li>Formal guidelines for integration of praziquantel and benzimidazole programming</li> </ul>	Cost-effectiveness modelling studies with support from feasibility studies <sup>10,18,31,32</sup>
<ul style="list-style-type: none"> <li>Validated strategy with trial data</li> </ul>	Trials underway
<ul style="list-style-type: none"> <li>Rigorous monitoring and evaluation strategies to detect emergence of drug resistance</li> </ul>	Statistical models with field validation <sup>49</sup>
<b>Step 2: Incorporate complementary interventions in the global strategy</b>	
<ul style="list-style-type: none"> <li>Water, sanitation, and hygiene (WASH) programming (e.g. community-led total sanitation)</li> </ul>	Systematic review and meta-analysis with mixed findings including mostly observational studies <sup>34-42</sup>
<ul style="list-style-type: none"> <li>Information, education, and communication (EIC) programmes</li> </ul>	Trial data <sup>40</sup>
<ul style="list-style-type: none"> <li>Snail control (for <i>Schistosoma</i> spp).</li> </ul>	Systematic review and meta-analysis including mostly observational studies; modeling studies <sup>15,43</sup>
<b>Step 3: Create distinct guidelines based on epidemiology, programmatic goals, and resource constraints</b>	
<ul style="list-style-type: none"> <li>Guidelines for a goal of morbidity control <i>versus</i> elimination of transmission</li> </ul>	Expert opinion

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401 **Table 1: Annual disease burden, mortality, and economic burden of current global strategy,**  
 402 **idealized WHO preventive chemotherapy guidelines, and cost-effective preventive chemotherapy**  
 403 **guidelines for schistosomiasis and STH**

Strategy	Disease burden (DALYs)	Mortality (DALYs)	Economic losses <sup>c</sup> (2015 US\$, thousands)
No treatment	4,156,306	176,393	6,482,613
Current global strategy <sup>a</sup>	3,957,325	176,392	6,182,450
Idealized WHO guidelines <sup>b</sup>	3,474,731	159,921	5,462,829
Cost-effective guidelines <sup>18</sup>	1,674,551	88,877	2,715,934
Cost-effective guidelines <sup>18</sup> relative to:	Avertable disease burden (DALYs)	Avertable mortality (DALYs)	Avertable economic losses <sup>c</sup> (2015 US\$, thousands)
No treatment	2,481,755	87,516	3,766,679
Current global strategy <sup>a</sup>	2,282,774	87,515	3,466,516
Idealized WHO guidelines <sup>b</sup>	1,800,180	71,044	2,746,895

404 <sup>a</sup>Estimation based on WHO guidelines with current global coverage for preventive chemotherapy.

405 <sup>b</sup>Estimation based on WHO guidelines with 75% coverage and uses school-based preventive chemotherapy  
 406 programmes, except for inclusion of preschool-aged children in STH treatment. This reflects the stated priority  
 407 within guidelines, the current global strategy, and empirical coverage estimated amongst different age groups.  
 408 However, WHO guidelines do recommend treatment of women of childbearing age for STH, and treatment in entire  
 409 communities under some circumstances above 50% prevalence for schistosomiasis, although coverage remains  
 410 minimal in these groups.

411 <sup>c</sup>Economic losses are estimated as the product of disability (DALYs) and country GDP per capita (see Appendix).  
 412 Note: Results are annualized over a 5-year simulation and are intended to give a broad estimate of the magnitude of  
 413 avertable health and economic loss. Methodological details, limitations, and discussions of uncertainty are provided  
 414 in the Appendix.  
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426 **Acknowledgements**

427 NCL dedicates this article to the inspirational memory of VUML.

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449 Contributors:

450 Mr. Nathan C. Lo had full access to all of the data in the study and takes responsibility for the  
451 integrity of the data and the accuracy of the data analysis.

452 Article conception- NCL

453 Data analysis- NCL

454 Contributed intellectual material and approved final draft - All authors

455

456 Declaration of interests:

457 The authors declare no conflicts of interest. All authors have reported through the ICJME form.

458

459 Funding/Support:

460 National Institutes of Health Medical Scientist Training Program (MSTP) - NCL; University of  
461 Georgia Research Foundation, Inc., funded by the Bill & Melinda Gates Foundation,

462 Schistosomiasis Consortium for Operational Research and Evaluation (SCORE) - DGC

463

464 Role of the Funding Organization or Sponsor:

465 The funding organisations had no role in the design and conduct of the study; collection,

466 management, analysis, and interpretation of the data; and preparation, review, or approval of the

467 manuscript; or the decision to submit the manuscript for publication.

468