

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

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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).^{1,2} 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’).³ 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.^{3,4} 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.^{5,6} Over this period, there
98 have been corresponding reductions in the number of infections and global disease burden

99 estimates.^{1,2,7} 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.^{8,9} 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.^{8,10,11} 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.¹² 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.^{3,4,13} 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.^{10,13-16} The
130 relative advantage of community-based treatment has been further supported by a recent
131 systematic review and meta-analysis of observational studies.¹⁷ Furthermore, expanded
132 community-wide treatment can be highly cost-effective because of this averted morbidity, even
133 if transmission is not eliminated.^{10,18} 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.^{19,20}

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.^{3,4} 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.^{10,18} 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.¹⁸ 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.¹⁸ 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.²¹ 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.²²⁻²⁴
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.²⁵

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).²⁶⁻³⁰ 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.^{10,16,17}

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.^{10,18,31,32} While integrated preventive chemotherapy
175 guidelines do exist, improving country-level coordination of these programmes would benefit
176 cost-efficiency.^{18,33} 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.^{10,31} 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.³² 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.³⁴ 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.³⁵⁻³⁹ However, the experimental
199 evidence from trials is mixed, and studies are ongoing to validate the data from observational
200 studies.^{37,39,42} Regardless, these programmes are likely to have substantial spillover benefit by
201 reducing the incidence of other infectious diseases improving country-level cost-effectiveness.³⁹

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.^{15,43,44} 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.⁴⁵ 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.⁴⁶

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.⁴⁷

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 helminthiasis 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
Step 1: Update strategy for preventive chemotherapy	
<ul style="list-style-type: none"> Expanded treatment across broader age groups (i.e., community-wide treatment) 	Modelling and cost-effectiveness studies ^{10,14,18,48} with support from systematic review and meta-analysis of observational studies ¹⁷
<ul style="list-style-type: none"> Lower prevalence thresholds for treatment, especially for schistosomiasis 	Modelling and cost-effectiveness studies ¹⁸ with support from observational studies
<ul style="list-style-type: none"> Formal guidelines for integration of praziquantel and benzimidazole programming 	Cost-effectiveness modelling studies with support from feasibility studies ^{10,18,31,32}
<ul style="list-style-type: none"> Validated strategy with trial data 	Trials underway
<ul style="list-style-type: none"> Rigorous monitoring and evaluation strategies to detect emergence of drug resistance 	Statistical models with field validation ⁴⁹
Step 2: Incorporate complementary interventions in the global strategy	
<ul style="list-style-type: none"> Water, sanitation, and hygiene (WASH) programming (e.g. community-led total sanitation) 	Systematic review and meta-analysis with mixed findings including mostly observational studies ³⁴⁻⁴²
<ul style="list-style-type: none"> Information, education, and communication (EIC) programmes 	Trial data ⁴⁰
<ul style="list-style-type: none"> Snail control (for <i>Schistosoma</i> spp). 	Systematic review and meta-analysis including mostly observational studies; modeling studies ^{15,43}
Step 3: Create distinct guidelines based on epidemiology, programmatic goals, and resource constraints	
<ul style="list-style-type: none"> Guidelines for a goal of morbidity control <i>versus</i> elimination of transmission 	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 ^c (2015 US\$, thousands)
No treatment	4,156,306	176,393	6,482,613
Current global strategy ^a	3,957,325	176,392	6,182,450
Idealized WHO guidelines ^b	3,474,731	159,921	5,462,829
Cost-effective guidelines ¹⁸	1,674,551	88,877	2,715,934
Cost-effective guidelines ¹⁸ relative to:	Avertable disease burden (DALYs)	Avertable mortality (DALYs)	Avertable economic losses ^c (2015 US\$, thousands)
No treatment	2,481,755	87,516	3,766,679
Current global strategy ^a	2,282,774	87,515	3,466,516
Idealized WHO guidelines ^b	1,800,180	71,044	2,746,895

404 ^aEstimation based on WHO guidelines with current global coverage for preventive chemotherapy.

405 ^bEstimation 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 ^cEconomic 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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452 Article conception- NCL

453 Data analysis- NCL

454 Contributed intellectual material and approved final draft - All authors

455

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