

Public health policy pillars for the sustainable elimination of zoonotic schistosomiasis

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8 **ABSTRACT**

9 Schistosomiasis is a parasitic disease acquired through contact with contaminated freshwater.
10 The definitive hosts are terrestrial mammals, including humans, with some *Schistosoma*
11 species crossing the animal-human boundary through zoonotic transmission. An estimated
12 12 million people live at risk of zoonotic schistosomiasis caused by *Schistosoma japonicum*
13 and *Schistosoma mekongi*, largely in the World Health Organization's Western Pacific Region
14 and in Indonesia. Mathematical models have played a vital role in our understanding of the
15 biology, transmission, and impact of intervention strategies, however, these have mostly focused
16 on non-zoonotic *Schistosoma* species. Whilst these non-zoonotic-based models capture some
17 aspects of zoonotic schistosomiasis transmission dynamics, the commonly-used frameworks are
18 yet to adequately capture the complex epi-ecology of multi-host zoonotic transmission. However,
19 overcoming these knowledge gaps goes beyond transmission dynamics modelling. To improve
20 model utility and enhance zoonotic schistosomiasis control programmes, we highlight three pillars
21 that we believe are vital to sustainable interventions at the implementation (community) and
22 policy-level, and discuss the pillars in the context of a One-Health approach, recognising the
23 interconnection between humans, animals and their shared environment. These pillars are: (1)
24 human and animal epi-ecological understanding; (2) economic considerations (such as treatment
25 costs and animal losses); and (3) sociological understanding, including inter- and intra-human
26 and animal interactions. These pillars must be built on a strong foundation of trust, support and
27 commitment of stakeholders and involved institutions.

28 **Keywords:** *Schistosoma japonicum*, *Schistosoma mekongi*, NTD, epidemiology, economics, sociology, mathematical modelling,
29 zoonotic transmission

1 INTRODUCTION

30 Neglected Tropical Diseases (NTDs) predominantly affect communities in low- and middle-income
31 countries and impose a significant human, economic and social burden, thus perpetuating a cycle of poverty.
32 Schistosomiasis is caused by infection with parasitic worms of the genus *Schistosoma*. An estimated 240
33 million people are infected¹ and the disease is classified by the World Health Organization (WHO) as
34 an NTD. The main *Schistosoma* species responsible for human disease are *Schistosoma haematobium*,
35 causing urogenital disease, and *S. mansoni*, *S. japonicum*, and *S. mekongi* causing intestinal disease. They
36 differ in geographical distribution and host species they infect. *Schistosoma haematobium* and *S. mansoni*
37 mainly infect humans as the definitive host. *Schistosoma japonicum* (found in the Philippines, China and
38 Indonesia), and *S. mekongi* (Cambodia and Laos) use human and non-human mammals as definitive hosts,
39 driving zoonotic transmission. Over 12 million people are estimated at risk of zoonotic infection in Asia
40 with three million requiring treatment. Though vital to transmission, the number of animals at risk is
41 generally not reported² (1). The life-cycle of zoonotic schistosomes is maintained by human and animal
42 contact with contaminated freshwater sources, where the intermediate hosts (species-specific freshwater
43 snails) are present, and where the access to safe water and sanitation is limited (Figure 1). Infections can
44 occur through recreational, habitual and employment activities of humans, and watering or grazing of
45 animals. Human intestinal schistosomiasis symptoms range from abdominal pain, diarrhoea, blood in the
46 stool, to liver and spleen enlargement, cancers and death (2). There is a dearth of data regarding the clinical
47 impact of *S. japonicum* and *S. mekongi* in animals.

48 In January 2021, schistosomiasis was targeted for elimination as a public-health problem (EPHP) globally
49 in the WHO's *Road map for neglected tropical diseases 2021-2030* (3). This is achieved when the proportion
50 of heavy intensity infections (over 400 eggs per gram of stool by Kato-Katz diagnostic) is reduced below
51 1% (3). The cornerstone of schistosomiasis control in endemic areas is preventive chemotherapy with the
52 anthelmintic praziquantel. However, drug treatment alone is likely insufficient to reach elimination goals
53 since only a few infected individuals can maintain the transmission cycle (4). Significant gains towards *S.*
54 *japonicum* elimination have been achieved with integrated intervention approaches (including preventive
55 and selective chemotherapy, mollusciciding, health-education, sanitation and environmental improvement)
56 in countries such as China. Although transmission was interrupted in some provinces for over 10 years,
57 other provinces remained endemic, and re-emergence has recently been observed (5, 6, 7, 1). Progress
58 towards elimination seems to be slowing, with transmission still ongoing in many regions, and zoonotic
59 schistosomiasis remains a public-health problem, particularly in the Philippines (8).

60 Efforts have been largely concentrated on the more common non-zoonotic schistosomiasis. Data needs
61 have been reviewed for various NTDs (9) and models have been successfully used to inform control
62 strategies (10, 11). Nevertheless, zoonotic schistosomes pose a unique challenge to achieving EPHP as
63 multiple definitive host species contribute to transmission dynamics (12). The complexity of zoonotic
64 schistosomiasis must be captured by these models if they are to continue playing a major role in public-
65 health policy. Data on animal reservoirs need to be collected along with data on humans to adequately
66 calibrate the models. Historical and current modelling approaches to capture the dynamics of schistosomes

¹ Who.int. 2021. Schistosomiasis. [online] Available at: <https://www.who.int/news-room/fact-sheets/detail/schistosomiasis> [Accessed 27 November 2021].

² Who.int. 2021. Preventive chemotherapy (PC) data portal [online] Available at: <https://www.who.int/GlobalHealthObservatory> [Accessed 27 November 2021].

67 and zoonotic transmission are reviewed elsewhere (8). Here we discuss the challenges of collecting and
68 analysing data and developing models to inform control programmes, and how a One-Health approach,
69 recognising the interconnection between people, animals, and their shared environment (13), can improve
70 them. Our vision builds on three cross-cutting pillars that are vital to sustainable public-health policy: (1)
71 understanding epidemiology; (2) economic considerations; and (3) accounting for sociological aspects. All
72 pillars must stand on a strong foundation of trust and support, requiring involvement and commitment of
73 stakeholders and other involved institutions (14). We illustrate the three pillars framework for building a
74 sustainable control programme in the context of zoonotic schistosomiasis EPHP, where animal reservoirs’
75 contribution to transmission accompanies all pillars. Nevertheless, this framework can be applied to
76 improve public-health policy across diseases.

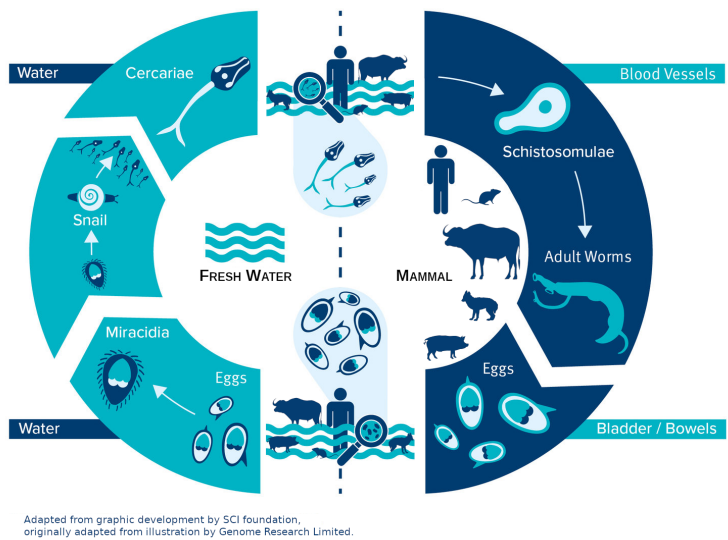


Figure 1. Life cycle of *S. japonicum* and *S. mekongi*. An infected definitive host, a mammal, passes *schistosome* eggs through the faeces into freshwater. The eggs may hatch into free-swimming larval miracidia that infect intermediate hosts, freshwater snails. After multiplication and development, snails shed free-swimming cercariae daily. The cercariae penetrate the skin of a mammal which comes in contact with water. Within the mammal, the cercariae shed their forked tail to form schistosomulae which mature and become worms. Paired male and female adult worms copulate and migrate to the mesenteric venules of the bowel and/or rectum where they lay thousands of eggs a day. Some of the eggs get back into the water through faeces and start the life cycle again, while some eggs get trapped in the organs causing disease symptoms.

2 PILLAR I: EPIDEMIOLOGY

77 This first pillar encompasses our understanding of the disease in its geographical context, including
78 environmental drivers, host heterogeneity, parasite interactions and intervention efficacy, derived from
79 a combination of epidemiological data (parasitological, surveys, etc.) and analyses. Prior to data
80 collection, mathematical modelling can inform on optimal study sample sizes, sampling frequencies,
81 and target participant groups necessary to accurately estimate parameters (15). Next, in collaboration
82 with stakeholders, optimal and accepted epidemiological and biological data collection can be undertaken
83 (16, 17, 18). To complete the understanding of disease transmission dynamics and to predict impacts of
84 interventions, mathematical models calibrated to, and informed by, available data provide quantitative

evidence, capable of informing both clinical trials and the final implementation of large-scale interventions, thus making these critical aspects of disease control more ethical and effective in the long-term. Model parameters and assumptions are based on field data, guided by stakeholder knowledge, in turn determining model quality (9).

Mathematical models have informed intervention programmes and played a vital role in informing the WHO's roadmap for NTDs 2021-2030 (19, 11). Model development and the coordination of necessary data collection should be conducted in consultation with stakeholders, who are ideally placed to understand and advise on local situations, expectations of modelled outputs, and optimal methods for data collection (14). Ensuring that modelling results are interpreted correctly, and that strengths and limitations of the models are recognised, requires communication at several structural levels. Introductory and follow-up meetings with institutions involved in policy decision-making, and discussions with stakeholders at community, district and national level (14) will result in the strongest interventions. Analyses focused exclusively on this first pillar can identify the most effective strategies to achieve a target health outcome and determine timelines for achieving them (20, 21, 22, 23).

It is widely acknowledged that to provide relevant insights, data quantity and quality needs to be improved (24). Specific data needs for some NTDs, including schistosomiasis, are reviewed elsewhere (9). The need for community-wide data is recognised, in particular, age-infection intensity profiles from adults – hindered because most studies focus on school-aged children. Low sensitivity and questionable specificities of available diagnostic tools (e.g. Kato-Katz and antigen-based diagnostics) also pose a challenge to data quality (25, 26). This becomes a greater problem as infection intensities are reduced after decades of preventive chemotherapy, further reducing the proportion of infections detected when egg-based diagnostics are the norm. Regarding interventions, if not applied yet, the lack of data can be overcome by making suggestions either based on data from different locations, or based on current interventions and expertise assumptions from stakeholders increasing uncertainty of modelled results. Many infection and population characteristics which influence disease transmission, such as present prevalence, age-intensity distributions, community- and age-contact rates and transmission rates, vary spatially. Therefore, studies mapping the spatial distribution in endemic areas need to be performed (27, 28, 29, 30, 31, 32). Furthermore, some biological aspects of infection and hosts cannot be, or are difficult to be, measured. For example, it is still not known what the dominant mechanism is behind age-intensity distribution – age-dependent water contact rate, acquired immunity, worm density dependence, concomitant immunity or (likely) some combination. These unknown aspects must be further explored (33, 34, 35, 36, 37).

Zoonotic transmission makes data collection and analyses more complicated. When human and animal data are collected independently, it becomes harder to consolidate and unify, hindering calibration and evaluation of multiple-host models. As highlighted by the WHO, providing centralised data access will facilitate understanding, expediting analyses and consequently the decision-making process (3). An example of this is the Pan-African Rabies Control Network, which established a platform for centralised rabies data collection and analysis, with an option for open data sharing (38, 39). We see opportunity in extending such a framework to other zoonotic diseases across a wider geographic area. Mapping the spatial distribution can help to identify locations and groups where efforts should be concentrated to prevent infection, improve interventions and increase coordinated communication across veterinary and human health teams (40).

In communities where zoonotic schistosomiasis is endemic, livestock can be a major asset, residing closely with owners. However, this also fosters an environment where domestic animals can be responsible for a considerable amount of transmission to humans (41, 4). Infection dynamics in these systems with multiple hosts differ significantly from single-host systems, and are more complex to model with greater

data requirements. Transmission rates vary across definitive host species, which can be due to differing behaviour like water contact, driving diversity in exposure and contamination rates. Similarly, each definitive host species will have different epidemiological characteristics in terms of recovery, birth, and mortality rates. Capturing definitive host heterogeneities in disease dynamic processes translates to more accurately predicting higher prevalences and intensities of infection (42, 43). Additionally, estimating the contribution of each definitive host species to parasite transmission is vital (19, 13).

The best combination of interventions is expected to vary spatially according to animal host species' densities. For example, in China, attention had initially been exclusively on bovines, because historically, most of the research was conducted in lake areas where bovines were ubiquitous (44, 41, 45, 46). It is known today that rodent species are the main animal hosts of *S. japonicum* in mountainous provinces, whilst bovines drive infection around the lakes (47, 4, 48, 49). To understand how to manage multi-host zoonotic systems, it is crucial to determine prevalence in animals and identify location-specific dominant animal reservoirs (50). Quantifying each host's contribution to transmission enables identification of maintenance and essential hosts, and the predicted impacts of control strategies targeting these hosts (51, 52, 53, 54, 55). Human-only treatment for schistosomiasis is insufficient to achieve EPHP in some settings because transmission is maintained by untreated reservoirs. Alternatively, interventions focused on the main reservoir predict success in reducing transmission to humans (4, 46, 49). Other work has explored the possible impact of a range of animal- and environment-focused controls (56, 46, 55). Different modelling approaches for the dynamics of intestinal helminths, including schistosomes and zoonotic transmission are reviewed elsewhere (8).

3 PILLAR II: ECONOMICS

The second pillar accounts for the economic implications of, in this case, different interventions to achieve EPHP. Primarily, a centralised data collection and analysis platform similar to that described above could reduce costs, as similar data needs across NTDs facilitate cross-cutting data collection and treatment activities (9). Furthermore, for an effective intervention strategy to be feasible, it must be affordable to individuals, governments and/or donors in addition to biologically effective. This includes the generally high upfront start-up investment, as well as recurrent maintenance costs. A useful economic evaluation approach is cost-effectiveness analysis, where costs and non-monetary health effects of different control interventions can be compared (57). Results are expressed as additional costs per unit of improved health outcome, such as reduction in transmission rate, prevalence/incidence, or deaths (58). The communication of results to policy-makers is key, as sometimes the most effective intervention for reducing disease might not be cost-effective (14). Cost-effective analysis has already been used for numerous NTDs and can be integrated into detailed infection transmission models. In the context of zoonotic diseases such as *S. japonicum* and *S. mekongi*, it should be leveraged to explore the costs and effectiveness of animal-based and other combined interventions (59). The costs to be considered include expected resources used for implementing and eventually maintaining an intervention, including the net savings to patients and healthcare providers due to reducing the disease burden (57). Savings comprise out-of-pocket and health system expenses, travel costs of care-seeking and opportunity costs of ill health, such as reduced patient productivity or school and work attendance, which are unfortunately often overlooked. In zoonotic schistosomiasis, additional costs are incurred due to animal death or illness, which adds time and cost to replace animals, as well as reduced livestock productivity (60).

One challenge remains regarding the appropriate metric to use for health outcomes that is generalizable. Disability-adjusted life-years (DALYs) are widely used to measure disease burden, with one DALY

171 representing the loss of one life-year lived in optimal health, thereby translating both disease mortality
172 (the years of life lost, YLL), and morbidity (the years lived with disability, YLD) into a single metric
173 (61, 62). This enables comparison across studies, settings, and interventions targeting the same or different
174 diseases (58). However, DALYs face some limitations, as they frequently disregard the infection-associated
175 mental health burden or the need to adjust for co-morbidities. To estimate morbidity, DALYs rely on
176 general estimates of disability weights – most of them estimated by an expert medical panel, instead of a
177 preference-based valuation method, raising universality concerns (63). This leads to the health impacts of
178 infection being underestimated. Lastly, DALYs are unsuitable when evaluating zoonotic diseases because
179 they disregard effectiveness resulting from improving animals’ and owners’ quality of life and well-being
180 due to averted animal morbidity/mortality. Efforts have been made to quantify the zoonosis burden on
181 humans and animals simultaneously – zoonosis disability-adjusted life-years (zDALYs) (64). These include
182 an additional component called animal loss equivalents, which converts expected livestock production and
183 local per capita income losses to the equivalent number of human YLD. Nevertheless, this metric has been
184 rarely used in cost-effectiveness analyses of zoonotic diseases (65, 66), and only once for schistosomiasis
185 (67).

186 Most economic evaluations of schistosomiasis interventions have focused on chemotherapy with
187 praziquantel (68, 69, 70). The WHO NTD roadmap has highlighted the benefits, including financial,
188 of cross-cutting interventions (3). However, the use of different effectiveness measures (i.e. health
189 outcomes) for evaluation of new control interventions hampers comparison within and between NTDs
190 (71, 72). Standardising the use of a common metric across economic analyses will enable cost-effectiveness
191 comparisons across multiple NTDs and beyond. Such metrics should be extendable, as appropriate to
192 zoonotic diseases. Programmes that consider the first and second pillars together are more sustainable, as
193 knowledge of the most effective interventions from an epidemiological perspective can be supplemented
194 by evaluations of their economic impact and the time horizon for cost benefits.

4 PILLAR III: SOCIOLOGY

195 The third pillar acknowledges the impact of human behaviour on intervention outcomes. This is most
196 commonly considered in the context of adherence, referring to how individuals interact with a given
197 intervention. For example, when offered medication, whether a person will ingest it or not, in the context
198 of animal treatment, whether an owner gives the drug to the animal – an important differentiation between
199 treatment coverage and treatment compliance (73, 36). If enough individuals do not adhere to control
200 measures, effectiveness at population levels can be lower than predicted. This can lead to failure in meeting
201 targets like EPHP and/or increases in intervention costs, which could change the cost-effectiveness of the
202 programme. Indeed, numerous studies across diseases (not just NTDs) suggest that it is not realistic to
203 expect full compliance with any control measure (74, 75, 76, 77, 78). Intervention strategies can be better
204 informed when models explicitly account for inconsistent adherers (79, 36).

205 Assessing the impact of novel interventions in a given location can be challenging when the social
206 determinants of participation are unknown. The WHO has suggested that Water, Sanitation, and Hygiene
207 (WaSH) methods should be incorporated into NTD control programmes (3). This will be crucial in the
208 context of zoonotic schistosomiasis where efficacy of WaSH interventions can be strongly affected by
209 non-compliance because very few individuals (human or animal) are required to maintain transmission.
210 Modelling the impacts of WaSH interventions is not novel for non-NTDs (80, 81, 82) or NTDs (83). Existing
211 studies focused on WaSH interventions to control schistosomiasis have been reviewed (84), and new studies
212 have been performed (85) or are currently ongoing (86). Interventions that include participatory processes

are more likely to be successful as people are more interested and perceive responsibility/ownership for the outcomes of the control programmes (87, 3, 88). Pre-intervention consultations with communities may help identify challenges in intervention design that can be addressed. For example, lack of clarity of ownership and maintenance obligations were reported as reasons to limit or halt usage of unmaintained boreholes (89). Quantification of preferences for different WaSH interventions can be obtained using discrete choice experiments (DCE) which enable the comparison of preferences for WaSH and health-education interventions, considering monetary and non-monetary costs (90). Health-education interventions can help people understand the transmission cycle, including animal contribution, and increase their perception of the disease threat, thus improving the adherence to WaSH and other interventions (90). Interventions informed by DCEs in areas endemic for zoonotic schistosomiasis will need to include preferences for animal-related interventions. The outcome of a strategy built on these pillars will provide more robust, sustainable policy recommendations.

5 DISCUSSION

Sustainability has been discussed in many fields, and always encompasses three pillars, environmental, economic, and social. Here, we have linked these three pillars in the context of NTDs, for the purpose of informing sustainable global-health policy. This is of particular importance for zoonotic NTDs (e.g. schistosomiasis caused by *S. japonicum* and *S. mekongi*), where the interconnection between people, animals, and their shared environment should be recognised – emphasising the importance of a One-Health approach. For the first pillar, epidemiology, we focus on definitive host heterogeneity and quantifying their contribution to overall transmission, enabling us to inform optimal intervention strategies and timelines to programmatic targets. Epidemiological understanding will be strengthened through access to improved cross-disease data. The second pillar, economics, can inform interventions by accounting for costs to all stakeholders involved and the time horizon for cost benefits. Challenges remain in establishing a standardised metric for cost-effectiveness evaluation that is appropriate for zoonotic diseases. The third, and last, pillar, sociology, considers the impact of human behaviour – particularly adherence – on programmatic success. A strong foundation of stakeholder engagement and commitment is needed from scientists across disciplines, politicians, and public-health experts. Only by combining these three pillars and commitment of all involved, can the best strategies to achieve the desired target health outcomes be developed, whilst considering costs, that will be championed by relevant stakeholders approved by local communities. The modelling community may use these recommendations to make the model predictions more accurate, assisting decision-makers to design sustainable control programmes to reach the WHO’s ambitious 2030 goal.

CONFLICT OF INTEREST STATEMENT

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

AUTHOR CONTRIBUTIONS

E. J. and J. M. P. conceived the study. E. J., J. C., O. K. wrote the original draft. All authors critically reviewed and edited the manuscript. J. M. P. provided overall supervision of the project.

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