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Public health policy pillars for the sustainable elimination of zoonotic schistosomiasis

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ABSTRACT

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

Keywords: ***Schistosoma japonicum*, *Schistosoma mekongi*, NTD, epidemiology, economics, sociology, mathematical modelling**

INTRODUCTION

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

The cornerstone of schistosomiasis control in all endemic areas is preventive chemotherapy with the anthelmintic praziquantel. However, drug treatment alone is likely insufficient to reach the elimination goal since only a few infected individuals are enough to maintain the transmission cycle (3). Significant gains towards *S. japonicum* elimination have been achieved with integrated intervention approaches (including preventive and selective chemotherapy, molluscicide, health education, sanitation and environmental improvement) in countries such as China. Nevertheless, although transmission was interrupted in some provinces for over 10 years, other provinces remained endemic, and re-emergence was also observed in the last few years (4, 5, 6, 1). The progress towards control and elimination seems to be slowing down, with transmission still ongoing in many regions, and zoonotic schistosomiasis remaining a public health problem, particularly in the Philippines (7). In January 2021, schistosomiasis was targeted for elimination as a public health problem (EPHP) globally in the WHO's *Road map for neglected tropical diseases 2021-2030* (8). This is achieved when the proportion of heavy intensity infections (over 400 eggs per gram of stool as per the Kato-Katz diagnostic) is reduced below 1% (8).

Zoonotic schistosome variants pose a unique challenge in achieving EPHP as they have multiple definitive host species contributing to transmission dynamics (9), which need to be more widely accounted for. Modelling efforts have largely concentrated on the more common non-zoonotic schistosomiasis, and have been successfully used to inform control strategies (10, 11). The complexity of zoonotic schistosomiasis must be captured by these models if they are to continue to play a major role in public health policy (7). Here, we discuss the challenges of developing such models, and how a One-Health approach recognising the interconnection between people, animals, and their shared environment, can improve control programmes

[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].

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(12). Our vision builds on three cross-cutting pillars that we believe are vital to sustainable public health policy, which we illustrate here in the context of zoonotic schistosomiasis EPHP; (1) understanding the epidemiology, (2) economic considerations, and (3) accounting for sociological aspects.

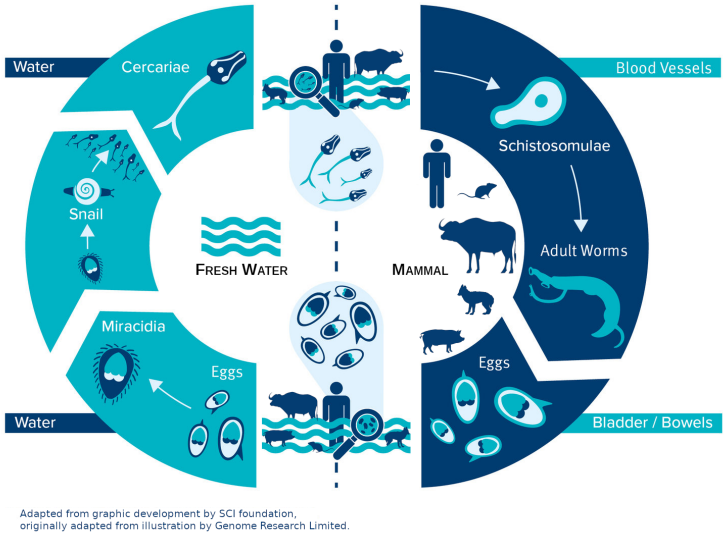

Figure 1. Life cycle of *S. japonicum* and *S. mekongi*. An infected definitive host, a mammal, passes *schistosome* eggs through the faeces into freshwater. The eggs may hatch into free-swimming larval miracidia that infect intermediate hosts, freshwater snails. After multiplication and development, 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.

PILLAR I: EPIDEMIOLOGY

This first pillar encompasses our understanding of the disease in its geographical context, including environmental drivers, host heterogeneity and parasite interactions. These can be informed through mathematical modelling which has provided quantitative evidence to inform intervention programmes and has played a vital role in informing the WHO's roadmap (13, 11). As a precursor to field trials, models ascertain long-term outcomes before implementing studies and control programmes, thus making them both more ethical and effective in the long-term. Analyses focused exclusively on this first pillar can identify the most effective strategies to achieve a target health outcome (14, 15, 16, 17).

In the context of communities where zoonotic schistosomiasis is endemic, livestock can be a major asset, residing closely with owners, fostering an environment where domestic animals may be responsible for a considerable amount of transmission to humans (18, 3). Infection dynamics in systems with multiple hosts differ significantly from single-host systems, and are therefore more complex to model. Transmission rates vary across definitive host species, which can be due to differing water contact behaviour, 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 these disease dynamic processes translates to more accurately predicting higher prevalences and intensities of infection (19, 20).

Additionally, estimating the contribution of each definitive host species to parasite transmission is vital (13, 12). 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 (21, 18, 22, 23). It is known today however, that various rodent species are the main animal hosts of *S. japonicum* in mountainous provinces, whilst bovines drive infection around the lakes (24, 3, 25, 26). The identification of location-specific dominant animal reservoirs and their transmission contributions to humans, along with model calibration to local data are evidently crucial (27, 28). Quantifying each host's contribution to transmission enables the identification of maintenance and essential hosts, and the predicted impacts of control strategies targeting these hosts (29, 30, 31). It has been shown that human-only treatment is insufficient to achieve EPHP because transmission is maintained by untreated reservoirs. Alternatively, interventions focused on the main reservoir predict success in reducing transmission to humans (3, 23, 26).

Some modelling work has explored the importance of a range of animal and environmental controls (32, 33, 23, 31). Nonetheless, for models to provide reasonable insight, data collection needs to be improved. In particular, 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 WHO, providing centralised data access will facilitate and expedite analyses, and consequently the decision-making process (8). An example of this is the Pan-African Rabies Control Network (PARACON), which established a platform for centralised rabies data collection and analysis, improving on the WHO recommendation with an option for open data sharing (34, 35). We see a great opportunity in extending such a framework to other zoonotic diseases across a greater geographic area. These enhanced resources will enable improved models that capture the epidemiology of the disease and inform intervention effectiveness and timelines to reach programmatic goals.

PILLAR II: ECONOMICS

The second pillar accounts for the economic implications of, in this case, different interventions to achieve EPHP. For the implementation of an effective intervention strategy to be feasible, it must be affordable to individuals, governments and/or donors. This needs to include the generally high upfront start-up investment, as well as recurrent maintenance costs. A useful type of economic evaluation approach for this is cost-effectiveness analysis, where costs and non-monetary health effects of different control interventions can be compared (36). Results are expressed as additional costs per unit of improved health outcome, such as reduction in transmission rate, prevalence/incidence, or deaths (37). This type of analysis has already been used for numerous NTDs and can be integrated into highly 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 (38).

The costs that need to be considered are the 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 (36). 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

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incurred due to animal death or illness, which adds time and cost to replace these animals, as well as reduced livestock productivity in quantity and/or quality (39).

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 representing the loss of one life-year lived in optimal health, thereby translating both the disease mortality (the years of life lost, YLL), and morbidity (the years lived with disability, YLD) into a single metric (40, 41). This enables comparison across studies, settings, and interventions targeting the same or different diseases (37). However, DALYs face some limitations, as they frequently disregard the infection-associated mental health burden or the need to adjust for co-morbidities. To estimate morbidity, DALYs rely on general estimates of disability weights – most of them estimated by an expert medical panel, instead of a preference-based valuation method, raising universality concerns (42). This leads to the health impacts of infection being underestimated. Lastly, DALYs are unsuitable when evaluating zoonotic diseases because they disregard the effectiveness resulting from improving animals' and owners' quality of life and well-being due to averted animal morbidity/mortality.

Efforts have been made to quantify the zoonosis burden on humans and animals simultaneously – the zoonosis disability-adjusted life-years (zDALYs) (43). These include an additional component called animal loss equivalents, which converts the expected livestock production and local per capita income losses to the equivalent number of human YLD. Nevertheless, this metric has been rarely used in cost-effectiveness analyses of zoonotic diseases (44, 45), and only once for schistosomiasis (46).

Most economic evaluations of schistosomiasis interventions have focused on chemotherapy with praziquantel (47, 48, 49). The WHO NTD roadmap has highlighted the benefits, including financial, of cross-cutting interventions (8). However, the use of different effectiveness measures (i.e. health outcomes) for the evaluation of new control interventions hampers the comparison within and between NTDs (50, 51). Therefore, standardising the use of a common metric across economic analyses will enable cost-effectiveness comparisons across multiple NTDs. Such metrics should be extendable, as appropriate to zoonotic diseases. Programmes that consider the first and second pillars together are more sustainable, as knowledge of the most effective interventions from the epidemiological perspective can be supplemented by evaluations of their likely economic impact.

PILLAR III: SOCIOLOGY

The third pillar takes into consideration the impact of human behaviour on intervention outcome. This is most commonly considered in the context of adherence, which refers to the way in which individuals interact with a given intervention, for example, when offered medication, whether a person will ingest it or not – an important differentiation between treatment coverage and treatment compliance (52, 53). In the context of zoonotic schistosomiasis, this can also refer to whether a person does indeed treat their animals. If enough individuals do not adhere to control measures, the effectiveness at the population level can be lower than predicted. This can lead to failure in meeting targets like EPHP and/or increases in intervention costs, which in turn, could change the expected cost-effectiveness of the programme. Unfortunately, but not surprisingly, numerous studies across diseases (not just NTDs) suggest that it is not realistic to expect full compliance with any control measure (54, 55, 56, 57, 58). Intervention strategies can be better informed when models explicitly account for inconsistent adherers (59, 53).

Assessing the impact of novel interventions in a given location can be challenging when the social determinants of participation are unknown. In the context of NTDs, the WHO has suggested that Water,

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Sanitation, and Hygiene (WaSH) methods should be incorporated into all programmes (8). This will be crucial in the context of zoonotic schistosomiasis where the efficacy of WaSH interventions can be strongly affected by non-compliance because very few individuals (human or animal) are required to maintain transmission. 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 (60, 8). Pre-survey consultations with communities may help identify challenges in intervention design that can be addressed with the survey. For example, lacking clarity of ownership and maintenance obligations was reported as a reason to limit or halt the usage of unmaintained boreholes (61). Quantitatively defined 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 cost in terms of monetary and non-monetary payment vehicles (62). Health education interventions can also help people understand the transmission cycle, including the contribution of animals, and increase their perception of the disease threat, thus improving the adherence of WaSH and other interventions (62). 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 three pillars will provide more robust, sustainable policy recommendations.

DISCUSSION

Sustainability has been discussed in many fields, and always encompasses three pillars, environmental, economic, and social. Here, we have linked those three pillars in the context of NTDs, for the purpose of informing sustainable global health policy. This is of particular importance in the case of zoonotic NTDs (like schistosomiasis caused by *S. japonicum* and *S. mekongi*), where there is a need to recognise the interconnection between people, animals, and their shared environment – 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, Social, considers the impact of human behaviour – particularly adherence – on programmatic success. Only by combining these three pillars can we develop the best strategies that achieve the desired target health outcomes, 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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