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Mathematical model of voluntary vaccination against schistosomiasis

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Human schistosomiasis is a chronic and debilitating neglected tropical disease caused by parasitic worms of the genus Schistosoma. It is endemic in many countries, in particular delete in sub-Saharan Africa. Although there is currently no vaccine available, vaccines are in development. In this paper, we extend a simple compartmental model of schistosomiasis transmission by incorporating the vaccination option. Unlike previous models of schistosomiasis transmission that focus on control and treatment at the population level, our model focuses on incorporating human behavior and voluntary individual vaccination.

We identify vaccination rates needed to achieve herd immunity as well as optimal, voluntary vaccination rates. We demonstrate that the prevalence remains too high (higher than 1%) unless the vaccination costs are sufficiently low. Thus, we can conclude that voluntary vaccination (with or without mass drug administration) may not be sufficient to eliminate schistosomiasis as a public health concern. The cost of the vaccine (relative to the cost of schistosomiasis infection) is the most important factor determining whether or not delete voluntary vaccination can yield the delete elimination of schistosomiasis. When the cost is low, the optimal voluntary vaccination rate is high enough that the prevalence of schistosomiasis declines under 1%. Therefore, delete Once the vaccine becomes available for public use, it will be crucial to ensure that the individuals have as cheap an access to the vaccine as possible.

The Abstract is appropriate and sets the scene for the manuscript very well.

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Mathematical model of voluntary [1] vaccination against schistosomiasis [2]

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ABSTRACT

Human schistosomiasis is a chronic and debilitating neglected tropical disease caused by parasitic worms of the genus Schistosoma. It is endemic in many countries, in particular in (delete) sub-Saharan Africa. Although there is currently no vaccine available, vaccines are in development. In this paper, we extend a simple (delete) compartmental model of schistosomiasis transmission by incorporating the vaccination option. Unlike previous models of schistosomiasis transmission that focus on control and treatment at the population level, our model focuses on incorporating human behavior and voluntary individual vaccination. We identify vaccination rates needed to achieve herd immunity as well as optimal voluntary vaccination rates. We demonstrate that the prevalence remains too high (higher than 1%) unless the vaccination costs are sufficiently low. Thus, we can conclude that voluntary vaccination (with or without mass drug administration) may not be sufficient to eliminate schistosomiasis as a public health concern. The cost of the vaccine (relative to the cost of schistosomiasis infection) is the most important factor determining whether or not voluntary vaccination can yield the elimination of schistosomiasis (substitute "the infection."). When the cost is low, the optimal voluntary vaccination rate is high enough that the prevalence of schistosomiasis declines to under 1%. Therefore, (delete) Once the vaccine becomes available for public use, it will be crucial to ensure that the individuals have as cheap an access to the vaccine as possible.

INTRODUCTION

Human schistosomiasis is a chronic and debilitating neglected tropical disease caused by parasitic flatworms of the genus Schistosoma (Ross et al., 2002). It is endemic in many countries in Africa, South America, and Asia (Madsen et al., 2022). Worldwide there are an estimated 800 million people at risk of infection (Steinmann et al., 2006); over 230 million people are infected with about 201.5 million living in Africa (Verjee, 2019).

Schistosoma genus consists of 23 species (Littlewood and Webster, 2017); we will focus on S. mansoni which is endemic throughout sub-Saharan Africa. The life cycle of Schistosoma mansoni is described, for example in McManus et al. (2018). The cycle involves an intermediate fresh-water snail host of Biomphalaria species (Habib et al., 2021) and the definitive human host. Eggs are excreted in the human faeces and they hatch upon contact with water. After hatching, the eggs release free-swimming ciliated larvae, miracidia which seek and penetrate the (delete) snail hosts. Within the snails, the parasites develop into sporocysts which reproduce asexually and Delete and substitute "to" produce numerous larvae, called cercariae. Cercariae (delete and substitute "The larvae" to avoid repetition of "cercariae") emerge from the (delete) snails in response to sunlight, and swim and (delete) seeking human hosts. Once cercariae penetrate the skin of a human host their tails drop off and the larvae transform into schistosomula. They enter the (delete) blood vessels and migrate to the liver, where they mature into adults. From the liver, the male and female worms migrate in pairs to the bowel. , where the (Delete) Females produces eggs which . Eggs (delete) are excreted in the (delete) faeces and the cycle continues.

Well written and accurately outlined.

Schistosomiasis control efforts include the following strategies: (1) disease treatment large-scale mass drug administration (MDA) of praziquantel (PZQ) (Doenhoff et al., 2009), (2) health education, (3) snail intermediate host control, and (4) water, sanitation, and hygiene (WASH) programs (Tchuente´ et al., 2017). Suggest listing the four strategies above.

Successes in Japan, China, Egypt and in some sub-Saharan African countries (Expand the country names involved in Sub-Saharan region) demonstrate that Control with progression towards elimination is possible (Rollinson et al., 2013). MDA by PZQ is a cost-effective

'preventive chemotherapy' and it is currently the strategy of choice and endorsed by WHO (Tchuente´ et al., 2017; WHO, 2021). However, this strategy is unsustainable in the long term and interruptions in these MDA programs can lead to rebounds of egg count (Ross et al., 2017). Vaccines are being developed, but none is (Rewrite as "are") available yet (Molehin et al., 2022; Molehin, 2020; Molehin et al., 2016). Mention why vaccines have not reached a state for use yet

Mathematical modeling plays a crucial and integral part of disease control and elimination (Anderson and May, 1992; Behrend et al., 2020). Many models exist for schistosomiasis transmission and control, including Woolhouse et al. (1996); Spear et al. (2002); Chiyaka and Garira (2009); Zhou et al. (2013); Mbah et al. (2014); Stylianou et al. (2017); Lo et al. (2018); Gurarie et al. (2018); Kadaleka et al. (2021b,a, 2022); Madubueze et al. (2022). In Collyer et al. (2019) and Kura et al. (2020), the authors modeled the impact of schistosomiasis vaccine. (Mention the impact envisaged) Other models focus on snail intermediate hosts (Woolhouse, 1991; Woolhouse and Chandiwana, 1990; Feng et al., 2002; Allen and Victory Jr, 2003; Zhao and Milner, 2008; Mangal et al., 2008; Anderson et al., 2021). In French et al. (2010), the authors fitted a model to data from a large-scale administration of PZQ in Uganda.

In this paper, we extend a compartmental model presented in Gao et al. (2011) which investigated the effect of MDA on schistosomiasis transmission. Inspired by Stylianou et al. (2017); Kura et al. (2019), we assume the vaccination is already available and focus on what happens when MDA and other control strategies are no longer in place. (Why would MDA and other strategies be stopped?) Specifically, we are interested to see whether the transmission can be substantially interrupted by voluntary vaccination.

Even if the vaccination is incorporated into existing pediatric vaccine programs and made mandatory, (Who will have the authority to mandate and what could be the consequences of failure to adhere to policy?) it does not automatically mean that the population would adhere to the mandates. Vaccine hesitancy and avoidance is a real concern in the US (Tolsma, 2015), Europe (Reczulska et al., 2022) as well as Africa (Anjorin et al., 2021). While vaccine hesitancy is well known in the West, how does that apply to African populations? There is a conflict between individual freedom and interests and the public health benefits (Paplicki et al., 2018). The vaccination produces herd immunity that can be enjoyed even by those not vaccinated (Serpell and Green, 2006). Thus, vaccination programs are prone to free-riding (Ibuka et al., 2014) because individuals maximize their self-interests, rather than the interests of the entire group (Maskin, 1999). (rewrite – further clarity needed)

We apply the game-theory framework popularized in Bauch and Earn (2004). The framework has been applied to many diseases; see Wang et al. (2016); Verelst et al. (2016); Chang et al. (2020) for recent reviews. As argued in (Wang et al., 2016), epidemics models incorporating human behavior provide more insight and better predictions. Thus, the game-theory models have been applied to study the prevention and elimination of many NTDs, mpox – (if the authors mean monkey pox, clarify. The others are sself -explanatory) (Bankuru et al., 2020; Augsburger et al., 2022; Augsburger et al., 2023), chikungunya (Klein et al., 2020), typhoid fever (Acosta-Alonzo et al., 2020), Chagas disease (Han et al., 2020), visceral leishmaniasis (Fortunato et al., 2021), lymphatic filariasis (Rychta´rˇ and Taylor, 2022), rabies (Campo et al., 2022), yellow fever (Caasi et al., 2022), or zika (Angina et al., 2022).

In the ideal case, the interests of the individual – to minimize one's costs, or to maximize one's benefits – align with the interest of the entire population – to reduce the prevalence of the disease below

an acceptable level. (Define a value for "acceptable.") If this is the case, by behaving optimally (in their own sense), the individuals will (will or should?)
behave optimally from the public health perspective. Thus, the individuals will more likely adhere to the mandatory vaccination policy and contribute to disease elimination as the public health concern. However, because the(delete) interests can differ, a behavior that is optimal from the perspective of an individual may not be optimal from the perspective of the group and vice versa. To avoid confusion, in the rest of the paper, when we say "optimal", we will mean optimal from the individual perspective, unless specified otherwise. The aim of this paper is to focus on incorporating human behavior and voluntary individual vaccination against schistosomiasis. We want to determine whether voluntary vaccination alone could eliminate schistosomiasis as a public health concern, i.e., decrease the prevalence of high intensity infections under 1% (WHO, 2021). (Rewrite as repetition from before)

MODEL

We introduce a mathematical model for voluntary vaccination against schistosomiasis. First, we incorporate a possible vaccination into a compartmental model of schistosomiasis transmission developed by Gao et al. (2011). Then, we add the game-theory (as opposed to "game-theoretical?" – this is used consistently in the manuscript but is not defined or cited) component that will allow us to investigate individuals' optimal vaccination decisions.

Compartmental model

The human population is divided into susceptible (S_1), infectious (I_1) and vaccinated (V_1). The snail population is divided into susceptible (S_2) and infected (I_2). The schistosomiasis pathogen is divided into (1) the snail-penetrating stage miracidia (M), and (2) the human-penetrating stage, cercariae (P). Human individuals are born susceptible to schistosomiasis at a rate L_1. Susceptible individuals become infected through contact with free-living cercariae present in contaminated fresh water. Because of saturating and crowding effect, we use a Holling type II incidence rate $\frac{b_1 P}{1+a_1 P}$ (Holling, 1959; Real, 1977), where b_1 is the rate of transmission in small concentrations of P and a_1 is a scaling factor. The infected humans are treated at rate h, returning back delete in delete to the susceptible population; without treatment the individuals stay infected.(Reference needed here to justify statement) Susceptible individuals are vaccinated at a rate n. Vaccinated individuals are assumed immune against the disease. They lose their vaccine-induced immunity at a rate w and become susceptible again. Infected humans may get vaccinated as well. From a practical standpoint, individuals with low intensity of infection will likely consider themselves susceptible and would vaccinate. Nevertheless, we assume that the vaccine does not work in these instances and the individuals stay infected. Hence, we do not consider a transition from I_1 to V_1 compartment. (Clarify this statement) Infected humans release parasite eggs giving rise to the population of mircacidia (Spelling – miracidia) M at rate g_1; we ignore the egg hatching period.

Susceptible snails are born at rate L_2. They become infected at a rate $\frac{b_2 M S_2}{M_0+eM_2}$ which is a Holling Type III incidence rate (Holling, 1959; Real, 1977), where b_2 is the rate transmission in small concentrations of M and M_0 and e are scaling factors. Infected snails give rise to the population of cercariae P at a rate, g_2. For simplicity, we assume that the risk of contracting schistosomiasis after the age μ_1^{-1} is negligible. Complex description but makes sense

Thus, all humans are removed from the population at risk at a rate μ_1 as they age. The infected cases also suffer from the disease-related death rate d_1; so they are removed from the population at a total rate μ_1+d_1. The susceptible snails die at a rate μ_2+q , where μ_2 is the natural death rate and q is the elimination rate of snails. Infected snails die at a rate μ_3+d_2+q , where d_2 is the disease-related death rate of snails. miracidia (M) die at a rate μ_3. The death rate of cercariae population P is μ_4+t where μ_4 is the natural death rate and t is the elimination rate. We ignore the negligible removal rates of miracidia and cercariae due to human and snail infections.

$$\frac{dS_1}{dt} = L_1 - \frac{b_1 P S_1}{1 + a_1 P} - \mu_1 S_1 + h I_1 - v S_1 + w V_1 \quad (1)$$

$$\frac{dI_1}{dt} = \frac{b_1 P S_1}{1 + a_1 P} - (\mu_1 + d_1 + h) I_1 \quad (2)$$

$$\frac{dM}{dt} = g_1 I_1 - \mu_3 M \quad (3)$$

$$\frac{dS_2}{dt} = L_2 - (\mu_2 + q) S_2 \quad (4)$$

$$\frac{dI_2}{dt} = \frac{b_2 M S_2}{M_0 + e M^2} - (\mu_2 + d_2 + q) I_2 \quad (5)$$

$$\frac{dP}{dt} = g_2 I_2 - (\mu_4 + t) P \quad (6)$$

$$\frac{dV_1}{dt} = v S_1 - w V_1 - \mu_1 V_1 \quad (7)$$

Table 1. Model parameters (top part) and other notation (bottom part) as based on Gao et al. (2011). The rates are per capita per year, the times are in years. The calibration procedure is described in section "Model calibration".

Symbol	Meaning	Value	Range	Source
L_1	Birth rate (humans)	0.031	[0.02,0.04]	World Bank (2022)
μ_1^{-1}	Max age of people at risk	20	[15,25]	Jordan (1972)
μ_2	Natural death rate (snails)	1.85	[1.5,2.4]	Appleton (1977)
μ_3	Natural death rate (miracidia)	1460	[1100,1750]	Maldonado et al. (1948)
μ_4	Natural death rate (cercariae)	830	[500,1100]	Whitfield et al. (2003)
g_1	Miracidia production rate	1.1×10^5	$[10^5, 2 \times 10^5]$	Alwan and LoVerde (2021)
g_2	Cercariae production rate	1.55×10^5	$[0.9 \times 10^5, 2.2 \times 10^5]$	Gabrielli and Garba Djirmay (2022)
d_1	Disease related mortality rate (humans)	10^{-4}	$[0, 10^{-2}]$	WHO (2021)
h	MDA treatment rate of humans	0	-	Assumed
t	Elimination rate of cercariae	0	-	Assumed
q	Elimination rate of snails	0	-	Assumed
n	Vaccination rate	variable	[0,0.1]	Assumed
w	Vaccine waning rate	1/6.5	[1/8,1/5]	Zhang et al. (2014)
d_2	Disease related mortality rate (snails)	0.25	[0,0.5]	Fitted
b_1	Human infection rate by cercariae	0.0013	[0.001,0.0015]	Fitted
a_1	Scaling factor for human infection rate	0.0315	[0.01,0.05]	Fitted
b_2	Snails infection rate by miracidia	12.71	[10,15]	Fitted
M_0	Scaling factor for snail infection rate	3500	[3000,5000]	Fitted
e	Scaling factor for snail infection rate	1.689	[1,2]	Fitted
L_2	Birth rate (snails)	10	[5,15]	Fitted
c	Cost of vaccine relative to cost of schistosomiasis	0.02	[0,0.1]	Assumed

d_1 Rate out of I_1 μ_1+d_1+h
d_2 Rate out of S_2 μ_2+q
d_3 Rate out of I_2 μ_2+d_2+q
d_4 Rate out of P μ_4+q
g Auxiliary variable
$L_1 g_1$
M_0
d Auxiliary variable $g_2 L_2$
a_2 Auxiliary variable e
M_0
5

Mathematical workings

Hence, the Nash equilibrium is given by (66), where S_0
$_1$ is given in (65), I_1 is given by (64), and $I_{2\,211}$ is
$_{212}$ given by (58). (The Nash equilibrium theory has ***not*** been explained or fully discussed, nor is it cited as a reference. It is critical to the whole manuscript) This is an omission to be corrected.

How do you calculate Nash equilibrium?

There is not a specific formula to calculate Nash equilibrium. It can be determined by modeling out different scenarios within a given game to determine the payoff of each strategy and which would be the optimal strategy to choose.

What are the limitations of Nash equilibrium?

The primary limitation of Nash equilibrium is that it requires an individual to know their opponent's strategy. A Nash equilibrium can only occur if a player chooses to remain with their current strategy if they know their opponent's strategy.

In most cases, such as in war—whether that be a military war or a bidding war—an individual rarely knows the opponent's strategy or what they want the outcome to be. Unlike dominant strategy, the Nash equilibrium doesn't always lead to the most optimal outcome. It just means that an individual chooses the best strategy based on the information they have.

Furthermore, in multiple games played with the same opponents, the Nash equilibrium does not take into consideration past behavior, which often predicts future behavior.

The Nash equilibrium can be applied in a variety of real-life situations to determine what the best payoff in a scenario would be, based on decisions as well as knowledge of another's decision.

$_{213}$ MODEL CALIBRATION

$_{214}$ We focus on transmission of S. mansoni and we locate as many parameters specific to this species
$_{215}$ as possible. However, since S. haematobium is also endemic in sub-Saharan Africa, some parameter
$_{216}$ estimates are based on that species or simply schistosoma species in general; we specifically say so if
$_{217}$ it is the case. We perform sensitivity and uncertainty analysis to account for possible discrepancies in
$_{218}$ parameter values.
$_{219}$ For birth rate, we will use a country in sub-Saharan Africa, like Zimbabwe where schistosomiasis in
$_{220}$ general is endemic (Midzi et al., 2014). In Zimbabwe, the birth rate is 31 births per 1,000 people per year
$_{221}$ (World Bank, 2022), i.e., $L_1 = 0.031$.
$_{222}$ The egg output of cases infected by S. haematobium (Bradley and McCullough, 1973) as well as the
$_{223}$ length of water contact (Jordan, 1972) varies by age and there is a sharp drop off after the age 20 for both
$_{224}$ measures (Kura et al., 2021). We will thus assume the same is true for S. mansoni and consider the aging
$_{225}$ rate $\mu_1 = 1/20$.
$_{226}$ We will consider snails of the Planorbidae family, especially Biomphalaria species, as they are one

are a common intermediate host of schistosomiasis (Gabrielli and Garba Djirmay, 2022). Their life span ranges between 5 to 8 months (Appleton, 1977) and we use the average death rate $\mu_2 = 12/6.5 \quad 1.85$ per year.

The longevity of S. mansoni miracidia is relatively small, about 5-6 hours and no more than 9 hours (Maldonado et al., 1948). We will thus use $\mu_3 = 365/(6/24) = 1460$. Similarly, S. mansoni cercariae live on average about 10.5 hours with a range from 8-17 hours (Whitfield et al., 2003) and so we set ($\mu_4 = 365Å{\sim}24/10.5 \quad 830$). We note that the cercariae may survive up to 72 hours (Nelwan, 2019).

S. mansoni females release about 300 eggs per day (Alwan and LoVerde, 2021; Mooee et al., 1956); we will thus use $g_1 = 300 \quad 365 \quad 1.1Å{\sim}10^5$.

The number of S. mansoni cercariae produced daily is 250–600 (Gabrielli and Garba Djirmay, 2022). We will thus use $g_2 = 425 \quad 365 \quad 1.55Å{\sim}10^5$.

We estimate the disease related mortality as $d_1 = 1/10^4$ based on 2016 global schistosomiasis data of 24,000 deaths and 240 million infections (Gabrielli and Garba Djirmay, 2022; WHO, 2021). This is in general agreement with Kheir et al. (1999) who estimated the annual mortality between $50/10^5$ and 1/1000 (or higher for specific kinds of infections.

There is currently no vaccine (Molehin et al., 2022) for humans. Nevertheless, based on phase 1 clinical trials in baboons, the longevity of one of the tested vaccines is 5-8 years (Zhang et al., 2014). We thus set the vaccine waning rate to be $w = 1/6.5$. The vaccine reduces the parasitic female load by about 90%, but for simplicity we will assume a complete protection.

For the purpose of the model, we will assume $h = 0$ because PZQ helps to control morbidity by killing adult schistosomes but it is ineffective against juvenile worms (McManus et al., 2018; Hagan et al., 2004). We also assume $c = 0.02$ with the range [0,0.05], the cost of the vaccine is about 1/50 of the cost of contracting schistosomiasis (and somewhere between 0 and 1/20 of the cost of the disease).

To find the values of other parameters, we set the controls to 0, i.e., set $n = 0, q = 0, t = 0, h = 0$, and fitted the model predictions to observed data of (a) the reproduction number, $R_0 \quad p_4 4.31$ based on Woolhouse et al. (1996), (b) the proportion of infected individuals, $I_1/(I_1+S_1) \quad 0.227$ based on Midzi et al. (2014), and (c) the proportion of infected snails $I_2/(I_2+S_2) \quad 0.018$ based on Odongo-Aginya et al.

Figures 2, 3, 4, & 5, are appropriate, and representative.

CONCLUSIONS AND DISCUSSION

We extended the compartmental model of schistosomiasis transmission (Gao et al., 2011) by adding the possibility of vaccination (Molehin et al., 2022; Stylianou et al., 2017) and applied the game-theoretic framework (Bauch and Earn, 2004). Unlike previous models of schistosomiasis transmission that focused on control and treatment at the population level, our model focuses on incorporating human behavior and voluntary individual vaccination.

We identified vaccination rates needed to achieve the herd immunity as well as optimal (from the individuals' perspective) voluntary vaccination rates. We evaluated the prevalence of schistosomiasis for the scenario when everyone uses the optimal vaccination rates. We demonstrated that the prevalence remains too high (higher than 1%) unless the vaccination costs are sufficiently low. Thus, we can conclude that the voluntary vaccination alone may not be sufficient to eliminate schistosomiasis as a public health concern. When combining vaccination with MDA, the elimination is feasible; however, in such scenarios, the elimination would be possible by MDA alone.

We calibrated our model based on the data from literature. However, especially data related to transmission rates were lacking and we thus had to fit our model numerically to empirical data. We argue that there is an ongoing need to strengthen data collection and evaluation for decision-making (Toor et al., 2021). We also performed uncertainty and sensitivity analysis and showed that the results are relatively robust; the optimal voluntary vaccination (without MDA) will not eliminate schistosomiasis in at least 65% of the scenarios. With MDA, the situation is somewhat better, the elimination would occur in all but 25% of the scenarios. Good explanation.

The cost of the vaccine for the individual was an important factor determining whether or not voluntary vaccination can yield the elimination of schistosomiasis. When the cost is low, the optimal voluntary vaccination rate is high enough that the prevalence of schistosomiasis declines under 1% and the disease is thus eliminated as a public health concern. Who is responsible for the vaccine cost in Africa? If it is not provided gratis, it is almost doomed to failure as a philosophy in Sub-Saharan Africa where nations are economically stressed. There is a big assumption here. Once the vaccine becomes available for public use, it will

therefore be crucial to ensure that the individuals have as delete cheap access to the vaccine as possible. delete
Our main finding that voluntary vaccination alone may not be enough to eliminate schistosomiasis is not surprising. These conclusions had been already reached in a general scenario (Geoffard and Philipson, 1997) as well as demonstrated for specific diseases with a high cost of vaccination relative to the cost of the disease such as cholera (Kobe et al., 2018), Hepatitis B (Chouhan et al., 2020; Scheckelhoff et al., 2021), lymphatic filariasis (Rychta´rˇ and Taylor, 2022), polio (Cheng et al., 2020), or typhoid fever (Acosta-Alonzo et al., 2020).
The big caveat of our quantitative results, though, is that, for simplicity, our model did not incorporate several important feature of schistosomiasis. First, the age is an important factor influencing the water contact and infection rates (Kura et al., 2021), but we considered it only marginally. To properly delete incorporate the age-dependent water contact properly, we would have to stratify the human population by age groups. This stratification would also allow better tracking of the prevalence of the infections amongst school age children, which is crucial for the WHO's elimination goal. The age groups would play an important role even from the logistical standpoint. Similarly to MDA which is administered mostly to school age children needs rewording (King et al., 2011), it seems that the vaccine would have to be administered before age
5 by incorporating into existing pediatric vaccine programs. Due to waning protection, the vaccination would have to be reapplied delete. Use "administered." every 5 or so years. However, these aspects were not addressed by our model Admission of weakness in achievement, but no other suggestions inserted.
at all. Delete
Second, we assumed that delete the vaccine offers 100% protection while the real efficacy will be likely around 90% (Zhang et al., 2018). Nevertheless, based on modeling of imperfect vaccine done for example in Reluga and Galvani (2011); Augsburger et al. (2023); Augsburger et al. (2022), as long as the vaccine is 85% or more effective, there are no big differences in model outcomes between perfect and imperfect vaccines. Furthermore, usage of S. mansoni-only vaccine would likely not be acceptable in sub-Saharan Africa as there are regions where both S. mansoni and S. haematobium are endemic. A model that accounts for both species at the same time would be needed to better understand what to do in those regions.
Third, individuals eventually reach immunity (Kura et al., 2021; Wilkins et al., 1984) and this was omitted in our model that concentrated on the young population only. While the recovered compartment should be added to the later iterations of the model, we believe its addition would not significantly alter the results.
Our model can be further improved in several other ways. The underlying compartmental model can be made more realistic by (a) adding "exposed" compartments to human and intermediate hosts

(such as in Anderson et al. (2021)), (b) considering the fact that delete. Use "why" instead. infected humans release eggs rather
than miracidia, and most importantly (c) specifically model the parasite load (such as in Woolhouse et al. (1996)). Also, schistosomiasis endemicity exhibits a great variation when even neighboring villages show vastly different levels of parasite loads (Carabin et al., 2005). The distribution of schistosoma infections are highly over dispersed among hosts, even within age groups (Bundy, 1988); this can have implications on how effective the vaccination program is in reality. Incorporating some sort of structural modeling network to epidemics, for example as done in Hadjichrysanthou and Sharkey (2015) would be helpful.
The game theory part of the model can be extended as follows. We assumed that every individual has the same risk of infection. However, the risk varies by age and by their behavioral pattern (M'Bra et al., 2018). Individuals thus have different risk perceptions (Poletti et al., 2011) and also base their decision on different social aspects (Xia and Liu, 2013). Therefore, it is often beneficial to use multi-agent-simulation (MAS) methodology (Iwamura and Tanimoto, 2018; Kabir and Tanimoto, 2019; Kuga et al., 2019; Kabir and Tanimoto, 2020) which allows more flexibility and realism. Furthermore, our model assumed the risk of contracting the disease to be the only cost associated with not-vaccination. If the vaccine is made mandatory, there can also be penalties for vaccine avoidance, possibly shrinking the gap between optimal voluntary vaccination level and the level required to achieve elimination. Finally, we assumed all individuals have perfect and full information. This is unlikely to happen in reality. However, the people will look up to their local leadership for advice and support. It is thus critical for the success of the vaccination campaign that the local leaders receive proper information about the disease and the available prevention methods.

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