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Review

Transmission Modelling for Human Non-Zoonotic Schistosomiasis Incorporating Vaccination: Guiding Decision- and Policymaking

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Abstract: Schistosomiasis, acquired by skin-penetrating cercariae of dioecious digenean schistosomes during freshwater contact, afflicts nearly 260 and 440 million people with active infections and residual morbidity, respectively. About 10 million women at reproductive age contract schistosomiasis during gestation every year. Acute schistosomiasis is characterized by pre-patent pro-inflammatory CD4+ T-helper 1 or CD4+ Th1/T-helper 17 reactivity against immature schistosomulae. Chronic schistosomiasis is dominated by post-patent anti-inflammatory CD4+ T-helper 2 reactivity against ova epitopes. Flukes co-exist in immunocompetent definitive hosts as they are capable of evading their defense mechanisms. Preventive measures should be complemented by vaccination, inducing long-term protection against transmission, infection, and disease recurrence, given the latest advancements in schistosomal vaccines. Vaccines become pivotal when considering constraints of chemotherapy, i.e., lack of protection against re-infection, and evolving resistance or reduced sensitivity. Transmission models for human non-zoonotic schistosomiasis incorporating vaccination available in PubMed, Embase and Web of Science up to 31 December 2023 are presented. Besides conceptual model differences, predictions meant to guide decision- and policymaking reveal continued worm harboring that facilitates transmission besides residual infections. In addition, increased susceptibility to re-infection and rebound morbidity, both shifted to later life stages following the intervention, are forecasted. Consequently, a vaccination schedule is pivotal that considers the optimal age for initial immunization, i.e., pre-schoolchildren or schoolchildren in a cohort-based or population-based manner, while incorporating potential non-adherers promoting ongoing transmission. Longevity over magnitude of vaccine protection to antigenic schistosomal moieties is crucial. Accounting for pre-acquired immunity from natural exposure, in utero priming in addition to herd immunity, and induced by chemotherapy is crucial. Combining, as a multi-component approach, long-term effects of vaccination with short-term effects of chemotherapy as regular repeated vaccine-linked therapy seems most promising to achieve WHO's endpoints of transmission elimination and morbidity control.

Keywords: *Schistosoma*; schistosomiasis; transmission dynamics; prediction; simulation; vaccination; policymaking

Citation: Panzner, U. Transmission Modelling for Human Non-Zoonotic Schistosomiasis Incorporating Vaccination: Guiding Decision- and Policymaking. *Parasitologia* **2024**, *4*, 101–128. https://doi.org/10.3390/parasitologia4020010

Academic Editor: Geoff Hide

Received: 26 February 2024
Revised: 27 March 2024
Accepted: 6 April 2024
Published: 15 April 2024

1. Epidemiology, Transmission, and Pathogenicity

Schistosomiasis, among WHO's neglected tropical diseases [1,2], is reported predominantly from tropical and subtropical countries. The helminthic disease, caused by dioecious digenean schistosomes within the platyhelminthes or flatworms, afflicts vertebrate hosts in presumably > 70 countries [2]. The blood-feeding flukes are responsible for approximately 260 and 440 million people with active infections and residual morbidity, respectively [3–8], and put nearly 800 million people at risk of infection [3–8].

Infestations in endemic settings commence among toddlers [9–11]. Parasitic loads augment during childhood, peak among adolescents [12–14], and decline during adulthood [9–11,15]. Notably, 60–80% schoolchildren and 20–40% adults suffer from persistent

infections [5,11,16,17]. Every year, schistosomiasis is contracted during gestation [18,19] by a quarter of nearly 40 million women of childbearing age carrying the flukes [20,21].

Species affecting mankind are *Schistosoma haematobium*, *S. mansoni,* and *S. japonicum* [22,23]. *S. mekongi*, *S. guineensis*, *S. intercalatum,* and *S. malayensis* impair humans less frequently [22,23]. *S. haematobium* and *S. mansoni* are seen throughout Africa and the Middle East [22–24]. *S. mansoni* is also reported from Latin America but *S. japonicum* solely from the Caribbean and Asia [22–24].

Clades of the genus *Schistosoma,* with geographical distribution, species, and species-specific intermediate invertebrate and definitive vertebrate hosts [25], are delineated in a report on natural human hybrid schistosomes [26]. Viable fertile interbreeds are found in West Africa with spreading to Central Africa, Eastern Africa, and Europe [26]. Natural and anthropogenic alterations, that derange species isolation [27,28] and promote bidirectional introgressive hybridization, cause new inter-species and inter-lineages among sympatric species. Hybrids' competitive extinction or homogenization with species [29,30] leads ultimately to new disease manifestation. Evolving recombinants due to their altered vigor are worrisome. It affects, e.g., virulence, transmission and infectivity, pathologies, maturation and fecundity, host spectra, and chemotherapeutic efficacy [29,31–41].

Infections of vertebrate hosts occur during freshwater contact infested with skin-penetrating cercariae that are disseminated by species-specific molluscs [26]. Cercariae transform into schistosomulae, and migrate via pulmonary, cardiac, and portal blood vessels to the hepatic vasculature [42]. They reach matured to schistosomes their oviposition sites within the mesenteric venules of the bowel/rectum or the venous plexus of the urinary bladder for pairing and sexual reproduction [42]. Schistosomes, capable of persisting in immunocompetent definitive hosts for decades [43], spend much of their lives in copula [44]. Despite the fact that they are monogamous, i.e., a single female fitted per male gynecophoric canal, competitive polygamic mating is possible [29,45]. This facilitates homo- and hetero-specific inter- and intra-species crossing in the hepatic portal system [46,47]. Ova deposited within venules of the portal and perivesical vasculature are transported towards the intestine or urinary bladder/ureters to be expelled purposefully via fecal or urinary routes. Once shed, the vertebrate-to-mollusc transmission for asexual reproduction continues upon miracidia hatching into freshwater [5,36,48–51].

Acute schistosomiasis among naïve hosts presents as debilitating febrile illness following an approximate 3-month incubation period [3,42]. Symptoms range from basic infectious disease signs to respiratory discomfort and hepato- and splenomegaly [3,42]. Chronic schistosomiasis manifests as immunoresponses to ova trapped in capillaries, leading to complications [2,52]. These include bleeding, scarring, inflammation [53], and granulomatous–fibrotic formations with species-dependent organ damage afflicting, e.g., liver, intestine, spleen, and the urinary bladder [3,23,26].

Intestinal schistosomiasis presents with diarrhea or constipation, including blood admixture and progression to ulcerations, hyperplasia, polyposis, and fibrosis. Urogenital pathologies manifest as dysuria, hematuria, and female genital schistosomiasis [54]. The latter impairs susceptibility to predominantly viral pathogens [55], and fertility, e.g., ectopic pregnancy and miscarriage, in addition to progression to malignancies, e.g., squamous cell carcinomas and sandy patches [44,56–59]. Notably, ectopic excess egg retention or erroneous worm migration in the central nervous system induces cognitive and physical impairments [60] that are seen in endemic settings [9,48,61].

2. Parasite and Human Host Responses

Intact schistosomes persist in the vasculature of immunocompetent definitive hosts for decades [62,63] since they adapt, modulate, and evade cellular and humoral immune defense mechanisms [5,53,64]. This is due to the tegument, a syncytial surface matrix covered with a lipoidal membranous bilayer pivotal for, e.g., metabolism, movement, and interchange [62,65–67]. The tegument enables the development from skin- and lung-stage immune-sensitive juvenile to adult immune-refractory stages through fre-

quent, rapid membrane alterations, in addition to modulation or masking of immunogenic molecules [5,11,64,66,68].

Infested hosts develop age-dependent partial protective immunity [13,17] to reinfection against moieties of dying worms [69–71], and initiate immunopathogenic immunoregulatory mechanisms against released ova antigens [9,61,72,73]. Notably, hosts' reactivity is impacted by, e.g., infection intensities [74], treatment history, co-infections [75], genetic pre-disposition, and in utero priming [14,48,76]. While larval stages and schistosomes are resistant to immune attacks [77], juvenile schistosomulae are their true targets [5,11,68].

Acute schistosomiasis presents as pre-patent, pro-inflammatory CD4+ T-helper 1 (Th1) or CD4+ Th1/T-helper 17 (Th17) responses [78] against immature schistosomulae. Elevated tumor necrosis factor alpha (TNF-α) and interferon gamma (IFN-γ) activate phagocytic cells to produce larvicides and cytokines [48,68,79–82]. Interleukin (IL)-17, for instance, stimulates neutrophils to release extracellular traps that sequester schistosomulae in the vasculature [48,68,79–82]. Regulatory CD4+ T-cells (Treg) stabilize immunoresponses and limit immunopathologies [83].

Chronic schistosomiasis is dominated by post-patent anti-inflammatory CD4+ T-helper 2 (Th2) reactivity [78] against ova epitopes [48]. Reactivity is augmented by antigen-presenting cells, members of the B7 superfamily, and cytokines to downregulate pro-inflammatory reactions [48]. IL-10 predominantly diminishes damage from Th1/Th2-mediated pathologies and polarizes Th1/Th2 responses, improving hosts' survival [79,80,84]. As extreme polarization is detrimental, the "happy valley" hypothesis states optimal host protection at either the Th1- or Th2-peak, where parasites feel "unhappiest" [79]. Th2-cells promote partial non-sterile resistance to reinfection [83]. Th2-cells also stimulate disease chronicity due to granulomatous–fibrotic formations mediated by cytokines in addition to signal transducer and activator of transcription/Stat6 pathways [83]. Pre-existing IgE occurs in the context of vaccine-induced hypersensitivity [83,85]. IgG4, IgG2, and IgM are associated with susceptibility to reinfection and disease severity, thus antagonists to protective antibodies [11,86–89].

Neonates of infested mothers possess anti-inflammatory Th2 responses [88,90] due to fetal exposure or in utero priming [16] to transplacentally crossed antigens [21]. Maternal IgG and IgG subclass immunoglobulins, fetal IgM and IgE indicative of immune system maturation, and proliferated cord blood mononuclear cells (CBMCs) [21,90,91] enable altered regulated postnatal reactivity and pathology, i.e., lower severity due to smaller granuloma, upon parasite challenge, e.g., sensitization or tolerization [11,48,76,90,92–94]. Effects are enhanceable by colostral and breast milk immunoglobulins [19,21,95–97]. Newborns of *S. haematobium*-infected Gabonese mothers had anti-ova IgE in their umbilical cord blood, reinforcing in utero priming [21,98,99]. Offspring of *S. mansoni*-afflicted Burundian mothers had complement-dependent cytotoxic antibodies in their umbilical cord blood comparable to maternal blood [99].

In utero-acquired immunity to maternal infection lasts 10–14 months and longer because of immunological memory even without booster challenges [91,100]. However, in utero sensitization occurs solely in about 50% of neonates [101]. This is due to variable maternal infection intensities [18] and offsprings' defects in cell cycle and cell proliferation/transcription pathways [20], as seen among Kenyan [102] and Gabonese [103] children of *S. mansoni*-infested mothers. Also, declines in proliferating maternal peripheral blood mononuclear cells assessed by CD3-4 and CD8 counts against ova, worms, and cercariae [21] leads to varying immunoreactivity dependent on the gestational status [88,90,97,98]. Chemotherapeutic boosting of maternal immunoresponse, still detectable at delivery, i.e., anti-worm IgE ($p = 0.054$) and IgG1 ($p < 0.001$), and anti-ova IgE ($p = 0.048$) and IgG4 ($p = 0.001$), is lacking in offspring [18]. This is likely due to sensitization prior to chemotherapy or impairment by maternal infection intensities, i.e., light infections promote while moderate and high infections prevent sensitization [18].

3. Treatment and Prevention

Globally, nearly 500,000 annual deaths are avertable [3,5,23,104,105]. The acylated quinoline-pyrazine or praziquantel (PZQ) is the chemotherapeutic in use [55]. PZQ acts poorly against juvenile [106,107] but well against adult schistosomes [7]. Disruption of the calcium homeostasis leads to muscle contractions, paralysis [108] and irreversible tegumental changes [16] in permeability and stability visible as blebbing, vacuolation, and cytoplasm leakage [16,109]. PZQ's effectiveness is influenced by parasite, e.g., vasculature localization [5,64,65,72,106,110–112], and host factors, e.g., infection intensity [74], immunoreactivity, exposure history, gut microbiota, physiological disposition, and bioavailability.

Upon administration, IgA, IgE, IgM, and IgG1-3 subclass immunoglobulins are detectable, inducing approximately 12 months' protection against re-infection. Protective effects are enhanceable, for instance, by eosinophils [113], and IgG4 promoting susceptibility to re-infection due to IgE blocking while modulating anaphylactic responses [7,16,114]. Regular repeated chemotherapy [52,113] reduces IgG4 titers [112].

Of concern is serious rebound morbidity [2]. It is caused by the re-emergence of missed immature worms upon irregular PZQ administration [43,115–119], seen as saw-tooth phenomenon [120], and evolving resistance [106,121] or reduced sensitivity [24,122]. The latter likely occurs due to genetic variability [123] or maturation of immature not fully eliminated parasite stages that are exposed to remaining sub-lethal drug concentrations [124–126].

The standard dose is efficacious against all species, though apparently better against *S. japonicum* over *S. mansoni* and *S. haematobium*, and mixed infections [115,127,128]. WHO's recommended treatment regimen is administered in a mass drug administration (MDA) [129] or selective at-risk manner [24,130,131]. The mode of treatment depends on prevalence, i.e., low or <10%, moderate or 10–50%, and high or ≥50%, and age, i.e., schoolchildren and adults. Diagnostic accuracy matters [24,71], as seen for nucleic acid tools detecting trace levels [132] that are reported subsequent to chemotherapy [132,133] and among apparently healthy individuals [42,134]. Pre-schoolchildren, at present, are unlikely to receive PZQ [128], due to paucity of efficacy and safety data [130,132,135]. Schoolchildren in low-risk settings receive PZQ twice during school time or once every three years, in addition to suspected cases [136]. Schoolchildren and at-risk adults, including women of childbearing age, are treated once every two years and annually in moderate-risk and high-risk settings, respectively [14,130,136,137].

Prevention includes [138] behavioral changes, health education, improved hygiene and sanitation, environmental and seasonal impacts [2,139–142], and eliminating freshwater molluscs [3,107,118,141,143–146]. Multi-component approaches [147–149] targeting humans and animals, i.e., in particular, water buffaloes among bovines [150–152] as sources of ongoing transmission [121,153], applied in endemic Asian settings, seem promising [151,154–159].

The early *S. mansoni* radiation-attenuated cercarial vaccine shortly elicited, post-immunization, long-lasting multi-species [160,161] CD4+ Th1/Th2 immunoresponses of >70% [52]. Building on this emphasizes the necessity to expand prevention by vaccination alone [7,16,162,163] to induce protection against transmission, infection, and disease recurrence [2,3,143,164], or combined with PZQ as vaccine-linked therapy [165]. Numerous antigenic moieties of, e.g., surface membranes, excretory/secretory proteins, tegument, cytosol, and gastrointestinal tract, detected by platforms ranging from initial schistosome saline extracts to the latest 'OMICS' [2,8], are still in the experimental stage [77,166].

Only a few candidates, though not on the market yet, advanced to clinical phases, i.e., Sm14 or *S. mansoni* fatty acid-binding protein (FABP) in ongoing phase II [2,8,167–169], Sm-TSP-2/Sm-TSP-2Al® or *S. mansoni* tetraspanin in phase I [170–174], Smp80/SchistoShield® or *S. mansoni* large-subunit calpain in ongoing phase I [52,175–177], and Sh28GST/Bilhvax® or *S. haematobium* glutathione S-transferase in phase III [60,178–182]. The latter was discontinued, lacking efficacy [165]. FABPs take up, transport, and compartmentalize host lipids, as schistosomes lack their own oxygen-dependent pathways to synthesize long-chain fatty acids and cholesterols [8,183]. Homologies in amino acid sequences with, e.g., *Echinococ-*

cus [2], *Clonorchis* [2], and *Fasciola* [2] demonstrate its cross-species multi-purpose vaccine potential [184–188]. TSPs, as scaffold proteins, are involved in immunoregulatory immunoevasive processes by absorbing host molecules to mask flukes' "non-self" status [189,190]. Phylogenetic polymorphism among protein–protein interacting extracellular mushroom-like loops of TSPs' large domain alters affinity and avidity to host immunoglobulins that causes varying protective efficacy [67,191–193]. Calpain, as a proteolytic protein, found in all schistosomal lifecycle stages, consists of a regulatory subunit that activates a catalytic subunit through a cascade of calcium-activated auto-proteolyses [194]. Calpain is relevant for tegumental biosynthesis and turnover [195] and has species-dependent structural differences in amino acid substitutions [196]. GST regulates, e.g., detoxification, antioxidant pathways, fatty acid metabolism, immune modulation, and neutralization of host-derived hydroperoxides [197]. Its crystal structure consists of two similar monomers, each having N- and C-terminal domains [198]. GSTs of *S. haematobium* and *S. bovis* exceed residue conservation within their domains, indicating protective cross-species potential [198]. A recent report delineates the candidates' developmental path, i.e., trial design, antigen properties and formulations, adjuvants, animal and human models, immunization schemes, and immunological, clinical, and safety endpoints [44].

An optimal vaccine induces non-sterilizing immunity and long-term ova reductions, preferably through killing of reproductive female worms while maintaining concomitant immunity against less-pathogenic single male worms [17,150,180,199,200]. Aimed for are reductions in worms and egg expulsion by $\geq$75% [9,10,77], as schistosomes are non-replicating in hosts [6,16,138]. Compatibility with therapeutics and vaccines of national immunization programs is desired [180,199].

4. Transmission Models

PubMed, Embase, and Web of Science databases were searched for transmission models tackling human non-zoonotic schistosomiasis through vaccination. See Table 1 for methodological details and models detected.

Initial mathematical modelling is traceable to Bernoulli in the 1760s [201]. Macdonald [50,138,148,202–207] and Barbour [152,202,208–211] developed early schistosomal simulations. Model aims are diverse, e.g., exploring transmission dynamics [212–215], worm mating probabilities [29,216], and programmatic as well as operational matters including resource allocation [217–220]. Predictions derived support, e.g., simulating novel hypotheses, designing vaccine trials [168,181,182,214], implementing interventions [17,201,207,210,221–226] that advance the flukes' control and elimination [107,131,136,144,220,227], and guiding decision- and policymaking [130,213,224,228,229].

Woolhouse's [230,231] construct delineates a phase II trial applicable to *S. haematobium* and *S. mansoni*. A partial protective vaccine with waning efficacy is administered Supplementary or complementary to natural immunity built from age-dependent parasite exposure [221].

Limited impact on the cumulative worm burden and increased susceptibility to re-infestation are predicted within a 30-year simulation period [201]. The latter results in rebound morbidity later in life [232], as opportunities to acquire natural immunity gradually and cumulatively [233] through trickle infections [29] are missed following the intervention. Consequently, what matters are the age of initial vaccination, with boosters throughout life, the parasitic targets of protective immunity, including magnitude of responsiveness to them [234], and vaccine effectiveness regarding duration, extent, and interaction with natural immunity [235].

Chan et al. [236] apply models, i.e., cohort model targeting pre-schoolchildren versus age-structured community-based model [223], to foresee the effects of an anti-establishment, anti-fecundity vaccine. Factors presumably impacting vaccine effectiveness relate to targeting naïve and previously or currently infested hosts as well as chemotherapy that induces additional antigen release.

Though both models show reductions in infection intensities, residual infection and parasite transmission and harboring likely continue [236,237]. Vaccinating once at an early age, inducing long-lived protection, or vaccinating repeatedly due to short-lived protection alters parasite transmission, which is impactable further when combined with MDA [238].

Chan and colleagues [239] simulate vaccine impacts on *S. mansoni* infection intensity and longevity of protection, including indirect effects or herd immunity [17], among a random infant and child population. Efforts combining vaccination with targeted or mass chemotherapy are assessed too. The partial differential density-dependent model [240] encompasses age-dependent parasite exposure [233,241], natural acquired immunity [71,117,240] that develops gradually and cumulatively [242,243] with waning upon reduced exposure [233], and vaccine-induced immunity directed at infestation and ova shedding. Vaccine protection reaches 75% and lasts 10 years on average. Chemotherapy reduces the per capita worm burden by 95%. Vaccine and drug coverage total 80% each [239].

Simulations reveal pivotal far-reaching reduced infection intensities subsequent to vaccinating the 1-year cohort and indirect effects of diminished transmission among the unvaccinated, indicating herd immunity. Outcomes are augmentable by prior MDA. A major finding attributable to vaccination and chemotherapy is a drift in peak infestations towards older ages. Immunizing the 7-year cohort or the 1-year and 7-year cohorts results in additional substantially declined infection intensities that are further expendable by chemotherapy. Taken together, duration over magnitude of vaccine protection and drug impact [244] is pivotal to determine the optimal age for interventions [240]. It needs to be considered that immunizing the youngest leaves them unprotected later in life, while immunizing schoolchildren protects them once they are at highest risk [239]. Also, repeated administration of interventions is required if effects are short-lived [17,116].

Building on classical macro-parasite modeling [138], Stylianou et al. [113] utilize a simple deterministic concept for assessing partial efficacious vaccine effects on dynamics of *S. mansoni* cercariae and worms, and hosts upon immunization [245]. Parasitic factors looked at are female fecundity and per capita mortality that impact mating and sexual reproduction. Hosts undergo annual infant immunization or mass immunization of random individuals from a homogeneous population. Including subjects afflicted by current or past parasite exposure raises concerns. Mating assuming monogamy [130,134,216,228], density-dependent ova expulsion [246], negative binomial distribution of schistosomes per host, and basic reproductive numbers (R_0) [17,247] are incorporated [113]. R_0 takes values of 1.0–1.4, 1.5–2.5, and >2.5, resembling low-, medium-, and high-transmission settings, respectively. Parasite-to-mollusc and parasite-to-vertebrate dynamics require weeks and several years, respectively [248].

Authors delineate that a 60% effective vaccine suffices to interrupt transmission in low and moderate settings. However, increased effectiveness or multiple annual boosters, equivalent to the approaches of Anderson et al. [249], are needed in high-transmission settings. The latter also applies if protection lasts less than 5–10 years. A vaccine addressing worm establishment and survival as well as female fecundity seems equally beneficial. In low-transmission settings, $\geq$18 years are required for breaking parasitic transfer. This is due to slow-building immunity and background mortality that both lower the proportion vaccinated and, thus, compromise herd immunity. MDA prior to immunization seems most beneficial. Combining human and animal MDA prior to vaccinating humans as well as bovines, as applied in endemic Asian settings [153,155], appears effective. This is because short- and long-term equilibrium prevalence, i.e., balanced prevalences or $R_0 < 1$, can be achieved, making schistosomal elimination more tangible [121,250].

Alsallaq et al. [248] employ an age-stratified, i.e., <4, 5–14, 15–24, and >24 years, deterministic compartmental model for *S. haematobium* based on a high-transmission Kenyan setting. They integrate exponential fecundity due to crowding or aggregation [25,249,251], and age-stratified worm burden, addressing chances of overdispersion [245]. A partial efficacious vaccine is included that targets worm accumulation and mortality [251] as well

as female fecundity, with 80% efficacy each, that lasts a decade or beyond two decades when combined with MDA. Vaccination is administered with/without MDA as a recurrent childhood campaign among naïve newborns, or mass vaccination while disregarding current or past parasitic exposure. PZQ kills worms with 75% efficacy within one month.

Predictions reveal that population-based mass vaccination and repeated mass or pulse vaccination over age-selective immunization is needed for short- and long-term impacts on schistosomal transmission, respectively [252]. Longevity of protection matters, similar to findings of Chan et al. [238] and Anderson et al. [249]. An optimal vaccine should preferably address the acquisition of cercariae that develop to schistosomes as well as the killing of established worms [164] to interrupt transmission. Combining mass chemotherapy with regular mass vaccination for optimized reduction in existing worms is most beneficial, which is demonstrated by dramatic declines in incidence rates [201], making schistosomiasis elimination appear more feasible.

Kura et al. [130,228] (Figure S1 Supplementary Materials) utilize an individual-based stochastic construct to forecast *S. mansoni* transmission [144,249]. Subjects receive MDA alone, assuming 86.3% efficacy, immunization alone, presuming 100% efficacy, and immunization combined with MDA. The vaccine is given to children $\leq$5 and $\leq$15 years in a cohort-based and community-based approach, respectively, including a single or repeated catch-up campaign [228]. Collyer et al.'s [253] individual-based stochastic model matches Kura's, except it contains 90% vaccine efficacy and 40% adult PZQ coverage. Graham et al.'s [254] flexible individual-based stochastic framework comprises chemotherapy for diverse transmission settings [148,155,222,237]. It enables adding immunization and molluscicide [148,155,222,237]. Kura's endpoints are WHO's 5% morbidity control and 1% transmission elimination [164] in low-, moderate-, and high-risk sites, as per WHO's prevalence classification. Endpoints are assessed within 300 simulations over a 15-year period. Disregarding temporary and permanent non-adherers [43,255] due to random real-life-like allocation of interventions risks ongoing parasite transmission [134,136]. Neglecting current and previous infestations may evoke adverse events [130,228].

Administering MDA alone to schoolchildren in low-risk settings requires 40% and 60% coverage to achieve morbidity control within 5-year (p = 0.987) and transmission elimination within 10-year (p = 0.923) periods, respectively. Toor et al. predict elimination within a 6-year time frame when presuming 75% coverage [136]. In moderate-risk sites, morbidity is controllable and transmission eliminable, i.e., interruption [133] or true elimination ($R_0 < 1$) [134,249], within 5 (p = 0.937) and 15 years (p = 0.960), but they require 60% and 75% MDA coverage, respectively. Toor et al. foresee elimination within a 10-year span assuming 75% coverage [136]. WHO's endpoints are hardly reachable in high-risk sites for other schistosomal species as well [136,256,257]. They could be tackled if frequency is increased, and coverage [258] reaches 75–85%, while including 40% of adults [136,144,164,253,259–261]. Notably, coverage needs adjustment to settings' risk level [14,130,164,260,261] when combined with other interventions [144,257].

Table 1. Schistosomiasis dynamic transmission models containing vaccination as intervening measure.

AUTHOR(S) Year [Reference]	WOOLHOUSE 1992/1995 [230,231]	CHAN et al., 1996 [236]	CHAN et al., 1997 [239]	STYLIANOU et al., 2017 [113]	ALSALLAQ et al., 2017 [248]	KURA et al., 2019/2020 [130,228]
SPECIES	*S. haematobium*/*S. mansoni* (other species)	Not stated	*S. mansoni* (other species)	*S. mansoni*	*S. haematobium*	*S. mansoni* (other species)
TARGET POPULATION	Small-scale (trial) population	Pre-school children vs. total age-structured population	Pre-school children aged 1 yr and 7 yrs (at-random administration)	Infants aged 1 yr (at-birth strategy, homogeneous population)	Total population age-stratified (≤4, 5–14, 15–24 and ≥25 yrs)	Total population age-stratified (≤4, 5–14 and ≥15yrs; constant number of deaths and births)
SETTING	Endemic	Endemic	Endemic	Low (R_0 1.0–1.4), medium (R_0 1.5–2.5), high (R0 > 2.5), endemicity	High endemicity	Low (<10%), medium (10–50%), high (≥50%) endemicity as per WHO's classification
MODEL DESCRIPTION	Phase II trial model	Compartmental cohort vs. transmission model	Differential compartmental density-dependent model	Simple deterministic compartmental model	Simple deterministic truncated compartmental model	Individual-based stochastic transmission model
MODEL DURATION	30 yrs	≥10 yrs	20 and 50 yrs	50 yrs	30 yrs	15 yrs
VARIABLES (e.g., larval infection, worm burden, mating, egg shedding)	• Age-dependent continuous Infection experience/rate (cumulative exposure to schistosomes or eggs) • Water contact rates peaking at hosts aged 17 yrs • Resistance to cercariae expressed as R_0 • Worm burden (mated female schistosomes per host as rate of infection; mean life-expectancy of schistosomes 4 yrs)	Not stated	• Age-dependent infection exposure/rate (reflecting acquired immunity; peak at 15 yrs of age) • Density-dependent rate of infection/transmission (doubling infection-less than doubling of transmission) • Mean life-expectancy of schistosomes 4 yrs • Worm burden translated into egg output per measurement unit	• Dynamic host-parasite populations via larval contact; rate of cercarial infection including grow to sexual mature worms/worm burden • Negative binomial distributions of adult worms per host/clumping factor/constant aggregation parameter • Density-dependent fecundity/egg output by female worms • Dynamics of life-cycle stages outside hosts (hours-weeks) vs. within hosts (4–6 yrs) • Mortality: hosts, parasites, free-living larvae • Mating probability • Monogamy • Mean parasitic load within community defined as weighted average of worms among vaccinated and unvaccinated • Flow of infectious material into environment • R_0 assessing spread and persistence among host population	• Varying age-dependent water contact and transmission rates • Rate of worm accumulation and fecundity dependent on host age; exponential fecundity decline by increasing parasite burden (crowding effect) • Dynamic worm distribution across age strata; stratified worm burden approach) • Baseline in vivo mortality rate of worms decreases with host age • Snail status (susceptible, pre-patent and patent) impacts snail density	• Concentration of infectious material in environment/host contribution to pool of released eggs; same as age-specific contact rates • Fast turnover of miracidia, snail intermediate host and cercaria (days to weeks) than adult worms in hosts (4–6 yrs) • Worm burden among target population as sum of worms in unvaccinated and vaccinated • Varying worm aggregation by host due to limited knowledge of environmental, social, genetic and immunological effects besides infection intensities; accounted for by specific contact rate by age category • Negative binomial distribution of parasites per hosts • Density-dependent fecundity • Monogamy • See Figure S1 Supplementary Materials for more information on model parameters

Table 1. *Cont.*

AUTHOR(S) Year [Reference]	WOOLHOUSE 1992/1995 [230,231]	CHAN et al., 1996 [236]	CHAN et al., 1997 [239]	STYLIANOU et al., 2017 [113]	ALSALLAQ et al., 2017 [248]	KURA et al., 2019/2020 [130,228]
VACCINATION	• Supplementary and complementary as postnatal campaign or at any age • 80–90% partial protective vaccine with 10-yr waning efficacy **Notes** • Immunological memory defined as duration of protection without continued exposure	• Cohort-based pre-school children campaign • Age-stratified mass population-based campaign • 90% partial protective vaccine with 20-yr waning efficacy	• 25%, 50%, 75% and 99% partial protective vaccine with 80% coverage and 10-yr waning efficacy **Notes** • Natural acquired immunity developing gradually based on cumulative schistosomal experience inducing partial protection; waning without continued exposure • Vaccine-induced immunity impacting infection rates, fecundity or worm establishment based on product properties; waning without continued exposure • Immunological pathways based on experimental animal models	• Cohort-based infant campaign • Population-based mass campaign • 80% partial protective vaccine with 85% coverage and 50-yr waning efficacy **Notes** • Differing parasitic life-cycle depending on maturation within/outside of immunized host • Age- and time-independent loss/waning of vaccine-induced immunity moves back vaccinated to unvaccinated • Instant vaccine-induced benefits among immunized individuals (no time delays) • Indirect impact of vaccination on infection intensity indicates herd immunity • Vaccine efficacy impacting various parasitic stages, e.g., fecundity and worm establishment	• Cohort-based continued naïve infant campaign • Population-based repeated mass campaign • 80% partial protective vaccine (each anti-susceptibility/-fecundity/-morbidity, therapeutic) with 100% coverage and 10-yr waning efficacy **Notes** • Age- and worm burden-independent vaccine efficacy targeting infection besides worm fecundity and accumulation; waning without continued exposure • Vaccinated returning to unvaccinated at an exponential rate given by the reciprocal of waning duration • Universal coverage across campaigns	• Cohort-based children campaign with catch-up campaign(s) • Population/Community-based mass campaign with catch-up campaign(s) • Vaccine of varying protective levels with high coverage and 5-yr, 10-yr and 20-yr waning efficacy **Notes** • Vaccine efficacy reducing rate of infection, parasite survival and growth within hosts, adult worm life expectancy, and rate of egg production
MDA/PZQ	Not administered	Single administration prior to vaccination considerable	• 95% instant *per capita* worm reduction and 80% coverage • Initial single administration during 1st yr	Not administered	75% instant *per capita* worm reduction over 28 days and 80% coverage	Varying species-dependent instant *per capita* worm reduction and age-related coverage

Table 1. *Cont.*

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PREDICTIONS/ FINDINGS	• Limited reduction in life-long cumulative worm burden • Increasing infection susceptibility; rebound morbidity at older age • Vaccination with repeated boosters throughout; parasitic targets inducing protective immunity relevant • Fully protective vaccine with rapid waning efficacy vs. low protective vaccine lacking waning efficacy	• Cohort campaign: reduced infection intensities despite substantial residual infections; MDA/PZQ supplementation recommended • Population campaign: minimal transmission reduction; initial MDA/PZQ with subsequent EPI vaccination recommended • Immunization prior parasite challenge recommended; optimal vaccine efficacy of long-lived/$\geq$15 yrs protection vs. short-lived protection with recurrent vaccine boosters	• Vaccine: reduced infection intensities across cohorts; herd immunity among unvaccinated • Vaccine & MDA/PZQ: substantially reduced infection intensities • Both, vaccination & MDA/PZQ shift in peak infection level towards older age due to residual transmission • Protective duration determines optimal age for intervening measures	• $\geq$60% vaccine efficacy, full coverage and $\geq$10-yr waning efficacy capable of interrupting transmission in low & moderate transmission settings; immunity & herd immunity build slowly • Higher efficacy, coverage and protective duration required besides annual boosters in high transmission settings; initial MDA/PZQ presumed beneficial • Vaccine effects equally beneficial disregarding the parasite target, i.e., worm survival, female fecundity, worm establishment	• Population campaign: declines in $\leq$87% egg shedding, infection intensity and worm acquisition; annual universal vaccination approaching elimination; vaccine & MDA/PZQ at 10-yr or 5-yr intervals impacting egg shedding, infection intensity and worm acquisition approaching elimination further • Cohort campaign: 5–24 yrs at-risk population or childhood campaign misses population fraction maintaining transmission • Protective duration determines optimal age for intervening measures	• Vaccine: WHO morbidity control achievable with high probability in low & moderate transmission settings with 5-yr and 20-yr protective vaccine; transmission elimination reachable with 5-yr and 20-yr protective vaccine, and 20-yr protective vaccine in low and moderate transmission settings, respectively; WHO goals unlikely achievable in high transmission settings • Vaccine & MDA/PZQ: WHO morbidity control achievable with high probability in low, moderate and high transmission settings with 5-yr and 20-yr protective vaccine; transmission elimination reachable with 5-yr and 20-yr protective vaccine in low and moderate but not high transmission settings • High impacts on morbidity control and transmission elimination by MDA/PZQ alone vs. vaccination alone in the short-term and long-term, respectively; MDA/PZQ & vaccination combined most promising reaching elimination when coverage and frequency augmented and targeted age groups expanded

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WEAKNESSES	• Small-scale population lacking applicability to overall transmission rates • Long-term follow-up required, e.g., ≥10 yrs • Epidemiological consequences at later age uncertain • Interaction of vaccine-induced immunity with natural acquired immunity uncertain • Uncertainties when administering immunization to currently and/or previously infected individuals (infection status) • Vaccine protective levels based on experimental animal models rather than human trials	• Applicability to *Schistosoma* species not clearly defined • Model parameters and its assumptions not clearly stated • Interaction of vaccine-induced immunity with natural acquired immunity uncertain • Uncertainties when administering immunization to currently and/or previously infected individuals (infection status) • Vaccine protective levels based on experimental animal models rather than human trials	• Long-term follow-up required, e.g., ≥15 yrs • Newborns targeted for childhood campaign disregarding the possibility of *in utero* priming • Interaction of vaccine-induced immunity with natural acquired immunity uncertain • Uncertainties when administering immunization and chemotherapy to currently and/or previously infected individuals (infection status) • At-random allocation of the intervention disregarding non-adherers and interactions between vaccine-induced and natural acquired immunity • Vaccine protective levels based on experimental animal models rather than human trials	• Worm lifespan in hosts 3.5–8 yrs impacting vaccine effects due to uncertainties on density dependence • Age-dependent infection rates derived from subjective, observed infection intensity and prevalence solely of *S. mansoni* • Wide range of potential vaccine efficacy for parasite parameters, i.e., infection, life expectancy, fecundity and establishment • Longevity of vaccine protection including indirect effects or herd immunity dependent on host mortality; impacts on mode of vaccine administration and target population, e.g., infants, pre-schoolchildren or schoolchildren • Vaccine protective levels based on experimental animal models rather than human trials; uncertainties of longevity of vaccine protection due to short-term experimental animal models • Newborns targeted for childhood campaign disregarding the possibility of *in utero* priming • Uncertainties when administering immunization to currently and/or previously infected individuals (infection status)	• Newborns targeted for childhood campaign considered naïve of infection; disregarding the possibility of *in utero* priming • Constant average number of snails over time disregarding seasonal variations impacting the force of infection to hosts • Seasonality disregarded throughout impacting endemicity and in turn prevention and control programs • Not applicable to other Schistosoma species due species-specific model parameters • Uncertainties when administering immunization and chemotherapy to currently and/or previously infected individuals (infection status) • Vaccine protective levels based on experimental animal models rather than human trials	• Values of model parameters taken from literature • Data for age-specific contact rates of hosts and age-specific contribution of hosts to the infectious reservoir lacking; application of MCMC/Markov chain Monte Carlo method for parameter estimation though impacting sensitivity of model findings • Case-perfect vaccine assumed, i.e., rates of infection and egg production reduced by 100%; prevention of worm establishment, fecundity falling dramatically and inability of egg hatching to release viable miracidia • At-random allocation of interventions disregarding non-adherers/non-compliance risking interactions between vaccine-induced and natural acquired immunity and over-optimize simulations as the proportion of non-adherers may be same across rounds of intervention • Limitation in performing predictions among low transmission/prevalence settings, i.e., <49%, caused by poor standard diagnostics and transmission dynamics • Build-up of acquired immunity and its impact on morbidity not incorporated in the model • Uncertainties when administering immunization and chemotherapy to currently and/or previously infected individuals (infection status) • Vaccine protective levels based on experimental animal models rather than human trials

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AUTHOR(S) Year [Reference]	WOOLHOUSE 1992/1995 [230,231]	CHAN et al., 1996 [236]	CHAN et al., 1997 [239]	STYLIANOU et al., 2017 [113]	ALSALLAQ et al., 2017 [248]	KURA et al., 2019/2020 [130,228]
STRENGTHS	• Simplified model in line with phase II trial • Applicable to several *Schistosoma* species • Flexibility of age/age group targeted	• Applicable to at-risk age-group and total age-structured population • Addition of chemotherapy possible	• Simulating scenarios of targeting children participating in Expanded Programme of Immunization (1 yr) and schoolchildren (7 yrs) • Applicable to several *Schistosoma* species possible • Addition of chemotherapy	• General framework allowing to assess different vaccine delivery strategies, i.e., infant and mass immunization including hybridale approaches; combining chemotherapy and vaccination • Assessing vaccine impacts on adult worm mortality, fecundity or establishment	• Stratified worm burden approach representing the process of worm accumulation and infection of snails • Impact of vaccine efficacies in reducing worm accumulation and fecundity of the transmission-contamination cycle • Addition of chemotherapy	• In part flexible, not constant parameter assumptions, e.g., worm aggregation among hosts, in line with the stochastic nature of the model • Model fitted to Iietune village, Kenya, but transferrable to other endemic settings though highly dependent on age-related contact and death rates, and prevalence • Model also transferable to *S. haematobium* • Addition of chemotherapy

Models by publishing author(s) and publication year, *Schistosoma* species, target population, setting, model description and duration, intervening measure(s), and predicted endpoints derived from latest searches in PubMed, Embase and Web of Science on 31 December 2023. The following search terms were applied: "schistosomiasis", "Schistosoma", "snail fever", "bilharzia", "katayama fever", "transmission", "modeling/modelling", "model", "vaccine", "vaccination", and "immunisation/immunization", "immunity" and "immune/immuno response". Publications enclosed after removing duplicates, screening titles and abstracts, reading full-texts, and complementing by reference searches were not limited by time period, but the availability of full-texts in English. Animal studies, reviews and conference notes were excluded unless considered highly relevant. Abbreviations: EPI = Expanded Programme of Immunization; yrs = years; yr = year; *S.* = *Schistosoma*; MDA = mass drug administration; PZQ = praziquantel; WHO = World Health Organization; vs. = versus; R_0 = reproductive number.

Immunizing 85% of 1-year-olds (cohort-1) and 60% of 5-year-olds (cohort-2) in low-risk settings, assuming 20-year protection, foresees achieving morbidity control and transmission elimination within 5 years (cohort-1: $p = 0.990$; cohort-2: $p = 1.000$), and 10 (cohort-2: $p = 0.920$) and 15 years (cohort-1: $p = 0.953$), respectively. The same schedule forecasts partial morbidity control within 15 years in moderate-risk (cohort-1: $p = 0.980$; cohort-2: $p = 0.987$) and high-risk settings (cohort-1: $p = 0.610$; cohort-2: $p = 0.550$), while transmission is ineliminable. Similar findings are predictable across settings, presuming 10-year protection and immunizing 85% of 1-year-olds and 60% of 5-year-olds each. Notably, this is achievable when combined with a catch-up campaign targeting 70% of 11-year-olds and 45% of 15-year-olds, respectively. Vaccinating 85% of 1-year-olds and 60% of 5-year-olds, assuming 5-year protection, foresees reaching morbidity control (cohort-5: $p = 1.000$; cohort-6: $p = 1.000$) and transmission elimination within 5 years (cohort-5: $p = 0.910$; cohort-6: $p = 0.943$) in low-risk sites. However, each cohort needs to receive two catch-up campaigns, i.e., 60% of 6-year-olds and 70% of 11-year-olds (cohort-5) and 70% of 10-year-olds and 45% of 15-year-olds (cohort-6), respectively. The same regimen administered to both cohorts in moderate-risk sites achieves morbidity control (cohort-5: $p = 0.943$; cohort-6: $p = 0.940$) and transmission elimination (cohort-5: $p = 0.953$; cohort-6: $p = 0.940$) within 5 and 15 years, respectively. While transmission is ineliminable in high-risk sites, morbidity is controllable partially among cohort-5 within 15 years ($p = 0.890$) [130]. Taken together, MDA has higher short-term effects on WHO's endpoints [129,260,262] while immunization impacts them in the long term [136,144,258]. This is because immunity, in particular herd immunity, takes time to develop. An optimal immunization strategy to control or even eliminate schistosomiasis depends on a setting's prevalence as well as vaccination age, vaccine coverage, and longevity of protection [201].

Vaccinating 85% of 1-year-olds and 60% of 5-year-olds, assuming 20-year protection, and administering MDA to schoolchildren, assuming 75% coverage, predicts achieving morbidity control and transmission elimination in low-risk settings within 5 years (cohort-1: $p = 1.000$; cohort-2: $p = 0.973$) and 5 (cohort-1: $p = 0.900$) and 10 years (cohort-2: $p = 0.960$), respectively. The same regimen applied in moderate-risk sites forecasts 5 years (cohort-1: $p = 0.993$; cohort-2: $p = 0.980$), and 10 (cohort-2: $p = 0.943$) and 15 years (cohort-1: $p = 1.000$) for controlling morbidity and eliminating transmission, respectively. Similarly, 10 (cohort-2: $p = 0.900$) and 15 years (cohort-1: $p = 0.970$) are predicted for controlling morbidity in high-risk sites, while transmission is ineliminable. Immunizing cohort-5 and cohort-6 assuming 5-year protection combined with 75% MDA coverage among schoolchildren appears most promising. Morbidity control (cohort-5: $p = 1.000$; cohort-6: $p = 1.000$) and transmission elimination (cohort-5: $p = 0.980$; cohort-6: $p = 0.987$) are forecasted within 5 years each in low-risk sites. Predictions are similar in moderate-risk settings, i.e., morbidity control (cohort-5: $p = 1.000$; cohort-6: $p = 1.000$) and transmission elimination within 5 years (cohort-5: $p = 0.983$; cohort-6: $p = 0.960$) each. In high-risk sites, morbidity is controllable within 5 (cohort-6: $p = 0.900$) and 10 years (cohort-5: $p = 1.000$) and transmission eliminable partially within 15 years (cohort-5: $p = 0.840$; cohort-6: $p = 0.820$). Collyer et al. [253] foresee that eradication is achievable within 15 years when vaccinating schoolchildren, and treating 75% schoolchildren and 40% adults in a community-based approach [164].

5. Model Considerations

In addition to conceptual model differences, predictions derived build on vaccines of varying protection and effectiveness. Vaccines are administered as age-stratified cohort-based or mass population-based regimens with variable coverage levels.

Simulations meant to guide decision- and policymaking reveal continued worm harboring that facilitates transmission and residual infections, though dependent on the risk level of a setting. Susceptibility to re-infection and rebound morbidity increases as opportunities to acquire natural immunity gradually and cumulatively are shifted to later life stages following the intervention.

Consequently, time points of vaccination, including potential boosters throughout life, are pivotal. Targeting pre-schoolchildren likely leaves them unprotected later on, while targeting schoolchildren probably protects them when they are at highest risk. Longevity over magnitude of protection to antigenic schistosomal moieties is crucial. This is because long-lived protection aims for a single vaccine administration, while short-lived protection requires repeated administration. Notably, interactions with natural immunity [2] also derived from in utero priming and indirect effects or herd immunity must not be disregarded. Combining long-term effects of vaccination with short-term effects of chemotherapy [121] as regular repeated vaccine-linked therapy in contrast to a sole intervention seems most promising to achieve WHO's endpoints.

Referring to vaccine candidates in clinical phases [44] reveals that Sm-TSP-2/Sm-TSP-2Al® [170–174], Sm14 [8,167,169,263,264], and Sh28GST/Bilhvax® [165,265,266] were tested in healthy and exposed adults, which is different to model constructs (Table 1). Only Sm14 [8,168] and Sh28GST [181,182] were also assessed among healthy and infested children.

Sm-TSP-2 Alhydrogel-adjuvanted was given to healthy, non-exposed American male and non-pregnant female adults aged 18–50 years in a phase I safety, reactogenicity, and immunogenicity trial with 12-month follow-up. A total of 30 ug and 100 ug over 10 ug rSm-TSP-2 induced the highest IgG titers at 4.5 months post-immunization, with waning at 5.5 months among all arms [172,173]. Sm-TSP-2/Alhydrogel was also administered to healthy, exposed Brazilian male and non-pregnant female adults aged 18–50 years in a phase Ib safety, reactogenicity, and immunogenicity trial with 12-month follow-up [171,174]. IgG and IgG subclass immunoglobulins, with IgG1 being preponderant across arms, peaked two weeks after administering the third dose. Antibody levels declined across arms at the end of follow-up, except for the 100 ug arm. Findings from immunizing healthy, exposed Ugandan male and non-pregnant female adults aged 18–45 years with Sm-TSP-2/Alhydrogel in a phase I/IIb dose escalation, safety, immunogenicity, and efficacy trial with 23-month follow-up are pending publication (trial status: active, not recruiting) [170].

Sm14 GLA-SE-adjuvanted was administered intramuscularly followed by two boosters to healthy, non-exposed Brazilian male and non-pregnant female adults aged 18–49 years during the phase I safety and immunogenicity trial with 4-month follow-up. It led to augmenting total IgG titers in 88% of subjects, commencing from the first booster on day 30, as well as IgG1-4 subclasses, while lacking IgE expression [263,264]. Findings from the Sm14/GLA-SE IIa dose escalation safety and immunogenicity trial with 3-month follow-up among healthy, exposed Senegalese male adults aged 18–45 years receiving a single pre-treatment with PZQ [167] are pending publication (trial status: completed). Healthy and *S. mansoni*- and/or *S. haematobium*-infected Senegalese children aged 8–11 years obtained Sm14/GLA-SE in a phase IIb safety and immunogenicity trial with 3-month follow-up subsequent to administering one pre-treatment with PZQ [169]; the findings are pending publication (trial status: completed).

Sh28GST Alhydrogel-adjuvanted was given subcutaneously to non-exposed Caucasian males aged 18–30 years in a phase I dose escalation, safety, tolerability, and immunity trial with 6-month follow-up. It elicited a preponderant IgG1 response over IgG2-4 subclasses following the first dose up to trial end, while IgA over IgE remained low throughout [265,266]. *S. haematobium*-infested Senegalese male and female children aged 6–9 years received, in a phase III2 safety, efficacy, pathology, and immunogenicity trial with 38-month follow-up, Sh28GST/Alhydrogel sub-cutaneously subsequent to three doses of PZQ pre-treatment [181,182]. The median follow-up without recurrence was 22.9 and 18.8 months among vaccinees and controls, respectively. At trial end, 86.4% of the vaccinated experienced $\geq$1 recurrence compared to 89.6% of controls. In the vaccine arm, total IgG titers were augmented up to month 65 and did not wane up to trial end. IgG1, IgG2, and IgG4 subclass immunoglobulins developed similar to total IgG, while IgG3, IgA, and IgE remained low throughout.

Adding short-term effects of PZQ to vaccination tackles schistosomes, further [115] seen as 76.7% (r = 0.434, p = 0.001) to 52–92% cure rate [267], and 86.3% (r = −0.126, p = 0.370) egg reduction rate [42,135]. Of note is the flukes' fluctuating susceptibility to the chemotherapeutic, i.e., strong shortly post-infection, weak ≤1 month post-infection, and strong again ≤2 months post-infection [109]. PZQ's properties are impacted additionally by previous treatment, i.e., best at first over multiple treatment doses [239,268]. Its administration to pre-schoolchildren as crushed tablets and syrup formulations may be considered, as it induces 87.3% (95%CI 85.7–88.2) and 82.0% (95%CI 72.6–90.0) cure rate, and 97.1% (95%CI 97.1–97.7) and 96.4% (95%Ci 72.6–90.0) egg reduction rate for *S. haematobium* and *S. mansoni*, respectively [269].

As raised by Anderson et al. [134], acquired protective immunity, i.e., widening of antibody spectra with switching from ova-specific IgM and IgG1-2 to larval- and worm-specific IgE [270] in juvenile and adult hosts, respectively, needs to be considered when making predictions to guide decision- and policymaking. This is because intervening measures [117] and natural exposure [242,271] as well as in utero priming [11,48,76] may alter immunoresponses. Interferences among tegumental and cytosolic antigens [108] released subsequent to PZQ and vaccine antigens is speculated to cause non-specific unwanted immunoresponses [16]. Also, Africans as opposed to Caucasians have more exhausted and activated natural killer cells, differentiated T- and B-cells, and pro-inflammatory monocytes [16]. Mediated immunity alters immunoprofiles that possess phenotypical and functional heterogeneity due to concomitant infections and genetic diversity [16].

In addition to enhancing efforts of vaccination and chemotherapy as multi-component approaches [109], health education in line with socio-cultural and ethnic contexts is capable of impacting human hosts' behavioral attitudes sustainably [134]. Pre-schoolchildren and schoolchildren from *S. mansoni* hyperendemic Marolambo, Madagascar, for instance, acquired better schistosomal understanding, i.e., 52–75% pre-education versus 83–98% post-education, and knowledge about preventive measures, i.e., 32–63% pre-education to 79–96% post-education [272]. Consequently, defecation into latrines over free-range and open water sources was practiced more often as well as minimizing water contacts [138,258], both associated to lower odds of *schistosomal* infestation [254]. Experiences from a long-lasting health educational program directed at Chinese aged 6–60 years from the high-transmission area of Poyang Lake revealed augmented schistosomiasis knowledge, i.e., 85.4% (p < 0.001) in schoolchildren and 29.5% (p < 0.001) in women [118]. Subsequently, water contacts by means of play and recreational activities and domestic chores declined, leading to reduced re-infections and prevalences by 83.7% and 63.4%, respectively. Effects were lower in males, likely due to occupational activities in agriculture and fishing.

Natural and, more importantly, anthropogenic environmental modifications raise concerns of breaking species isolation barriers [273] and derange dynamics and distributions of schistosomes [134,217,274]. Species sympatry and interplay, host switching or spillover through heterogeneous mixing [34], and expansion to new favorable habitats facilitated by altered fluke vigor [26,273] are likely consequences [273,275].

Examples are the construction of water dams at Senegal and Bafing rivers, Senegal [276], or Yangtze River, China [156], and irrigation channels in the Awash Valley, Ethiopia [277], as well as forest clearance and agricultural development at Loum, Cameroon [278]. Notably, Gurarie et al. [217,279] reported 1.1- and 4.7-fold increased risk of urinary and intestinal schistosomiasis, respectively, compared to non-irrigated settings. Destroying Madagascar's Dabara dam and adjunct irrigation channels reduced *S. mansoni* even without chemotherapy [217]. King et al. [278] demonstrated *S. haematobium* as the dominant species in Cameroon within 25–30 years subsequent to deforestation and agricultural expansion in the 1960s. Also, regular, prolonged molluscicide beyond the maximum worm life expectancy [248] by chemical and biological means, such as natural predators or competing organisms [109,134,258], impacts the schistosomal spread. Molluscicide combined with chemotherapy decreases novel infections and re-infections [280–282], e.g., from

12.5–40% to <9% in *S. mansoni* endemic Makueni, Kenya [283], except for insufficient ecological overlap [284].

Movement of seasonal migrant laborers or seminomadic pastoralists seen in Richard-Toll, Senegal and Awash, Ethiopia [277,285], and large-scale population re-settlements around the Three Gorges Dam, China [156] increase concerns. Interestingly, human migration between Senegal and Corsica/France for occupational opportunities likely re-introduced schistosomiasis to Europe in 2013 despite paucity in understanding the presence of *Bulinus* spp. and *Planorbarius* spp. molluscs [286,287].

6. Conclusions

Model predictions aiming to support decision- and policymaking towards 1% transmission elimination and 5% morbidity control demonstrate that only a multi-component approach containing vaccination will likely be capable to address the WHO's goals. Combining long-term effects of vaccination with short-term effects of chemotherapy as regular repeated vaccine-linked therapy seems most promising. Notably, vaccine effects in simulations are derived solely from experimental animal models rather than human trials. The population targeted for intervening measures needs to be selected in the context of the risk level of a setting, and the measures' parasitic targets, i.e., infection, fecundity, establishment and morbidity, and coverage, i.e., 40–80% for PZA MDA and 60–100% for vaccine, as well as efficacy, i.e., 75–95% for PZQ MDA and 15–100% for vaccine, and longevity of protection, i.e., 1–3 yrs for PZQ MDA and 10–50 yrs for vaccine. Notably, longevity over magnitude of protection is pivotal. Addressing pre-schoolchildren likely leaves them unprotected later in life, while directing measures at schoolchildren probably protects them when they are at highest risk. Administering chemotherapy additionally to around 40% of adults may enhance population-based effects. Vaccination as well as antiparasitic therapy needs to be given repeatedly, as demonstrated by simulations, including catch-up campaigns, as immunity in addition to herd immunity builds slowly. Notably, non-adherence or non-compliance constituting sources of ongoing transmission, and current and/or previous infections, as well as existing acquired immunity, must be taken into account to avoid adverse events.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/parasitologia4020010/s1, Figure S1: Simplified structure of the *Schistosoma mansoni* individual-based stochastic model illustrating interventions including coverage among targeted age categories.

Funding: This research received no external funding.

Conflicts of Interest: The author declares no conflict of interest.

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