Review

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

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Transmission Modelling for Human 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. Transmission models incorporating vaccination available in PubMed, Embase and Web of Science up to December 31, 2023 are presented. Besides conceptual model differences, predictions meant to guide decision- and policymaking reveal continued worm harboring facilitating transmission besides residual infections, and increased susceptibility to re-infection and rebound morbidity, both shifted to later life stages following the intervention. Consequently, a vaccination schedule is pivotal considering 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 including accounting for existing pre-acquired immunity from natural exposure, *in utero* priming besides herd immunity, and induced by chemotherapy. Combining as one multi-component approach long-term effects of vaccination with short-term effects of chemotherapy as regular repeated vaccine-linked therapy in contrast to a single-component intervention seems most promising for achieving WHO's endpoints of transmission elimination and morbidity control.

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

1. Epidemiology, transmission and pathogenicity

Schistosomiasis among WHO's neglected tropical diseases [1] 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. The blood-feeding flukes are accountable for approximately 260 and 440 million people with active infections and residual morbidity, respectively, and put nearly 800 million people at risk of infection [2–6]. Infestations in endemic settings commence among toddlers [7–9] with parasitic loads augmenting during childhood, peaking among adolescents [10–12], and declining during adulthood [7–9,13]; 60-80% schoolchildren and 20-40% adults suffer from persistent infections [4,9,14,15]. A quarter of nearly 40 million women of childbearing age carrying the flukes [16,17] contract schistosomiasis during gestation every year [18,19].

Species affecting mankind are *Schistosoma haematobium*, *S. mansoni* and *S. japonicum*; *S. mekongi*, *S. guineensis*, *S. intercalatum* and *S. malayensis* impair humans less frequently [20,21]. *S. haematobium* and *S. mansoni* are seen throughout Africa and the Middle East; *S. mansoni* is also reported from Latin

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America but *S. japonicum* soley from the Caribbean and Asia [20–22]. Clades of the genus *Schistosoma* with geographical distribution, species, and species-specific intermediate invertebrate and definitive vertebrate hosts [23] are delineated in a report on natural human hybrid schistosomes; viable, fertile interbreeds are found in West Africa with spreading to Central Africa, Eastern Africa and Europe [24]. Natural and anthropogenic alterations deranging species isolation [25,26] promote bidirectional introgressive hybridization causing new inter-species and -lineages among sympatric species; hybrids' competitive extinction or homogenization with species [27,28] leads ultimately to new disease manifestation. Evolving recombinants are due to their altered vigor worrisome; it affects e.g. virulence, transmission and infectivity, pathologies, maturation and fecundity, host spectra, and chemotherapeutic efficacy [27,29–39].

Infections of vertebrate hosts occur during freshwater contact infested with skin-penetrating cercariae disseminated by species-specific molluscs [24]. Cercariae transform into schistosomulae, and migrate via pulmonary, cardiac and portal blood vessels to the hepatic vasculature; they reach matured to schistosomes their oviposition sites within the mesenteric venules of bowel/rectum or the venous plexus of the urinary bladder for pairing and sexual reproduction [40]. Schistosomes, capable of persisting in immunocompetent definitive hosts for decades [41], spend much of their lives *in copula* [42]. Despite they are monogamous, i.e., single female fitted per male gynaecophoric canal, competitive polygamic mating is possible [27,43] facilitating homo- and hetero-specific inter- and intra-species crossing in the hepatic portal system [44,45]. Ova deposited within venules of the portal and perivesical vasculature are transported towards intestine or urinary bladder/ureters and expelled purposefully via fecal or urinary routes; once shedded, the vertebrate-to-mollusc transmission for asexual reproduction continues upon miracidia hatching into freshwater [4,34,46–49].

Acute schistosomiasis among naïve hosts presents as debiliating febrile illness following an approximate 3-months incubation period; symptoms range from basic infectious disease signs to respiratory discomfort and hepato- and splenomegaly [2,40]. Chronic schistosomiasis manifests as immunoresponses to ova trapped in capillaries leading to complications [50], i.e., bleeding, scarring, inflammations [51] and granulomatous-fibrotic formations with species-dependent organ damages, e.g., liver, intestine, spleen and the urinary bladder [2,21,24]. 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 [52]. The latter impairs susceptibility to predominantly viral pathogens [53], and fertility, e.g., ectopic pregnancy and miscarriage, besides progression to malignancies, e.g., squamous cell carcinomas and sandy patches [42,54–57]. Notably, ectopic excess egg retention or erroneous worm migration in the central nervous system induces cognitive and physical impairments [58] seen in endemic settings [7,46,59].

2. Parasite and human host responses

Intact schistosomes persist in the vasculature of immunocompetent definitive hosts for decades [60,61] since they adapt, modulate and evade cellular and humoral immune defense mechanisms [4,51,62]. This is due to the tegument, a syncytial surface matrix covered with a lipoidal membranous bilayer and pivotal for e.g. metabolism, movement and interchange [60,63–65]; it enables developing from skin- and lung-stage juvenile immune-sensitive to adult immune-refractory stages through frequent rapid membrane alterations besides modulation or masking of immunogenic molecules [4,9,62,64,66].

Infested hosts develop age-dependent partial protective immunity [11,15] to reinfection against moieties of dying worms [67–69], and initiate immunopathogenic immunoregulatory mechanisms against released ova antigens [7,59,70,71]. Notably, hosts' reactivity is impacted by e.g. infection intensities [72], treatment history, co-infections [73], genetic pre-disposition, and *in utero* priming [12,46,74]. While larval stages and schistosomes are resistant to immune attacks [75], juvenile schistosomulae are their true targets [4,9,66]. Acute schistosomiasis presents as pre-patent pro-inflammatory CD4+ T-helper 1 (Th1) or CD4+ Th1/T-helper 17 (Th17) responses [76] against immature schistosomulae with elevated tumor necrosis factor alpha (TNF-α) and interferon gamma (IFN-γ) activating phagocytic cells to produce larvicides and cytokines; interleukin (IL)-17 for instance stimulates neutrophils to release extracellular traps that sequester schistosomulae in the vasculature [46,66,77–80]. Regulatory CD4+ T-cells (Treg) stabilize immunoresponses and limit

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immunopathologies [81]. Chronic schistosomiasis is dominated by post-patent anti-inflammatory CD4+ T-helper 2 (Th2) reactivity [76] against ova epitopes augmented by antigen-presenting cells, members of the B7 superfamily, and cytokines to downregulate pro-inflammatory reactions [46]. IL-10 predominantly diminishes damage from Th1/Th2-mediated pathologies, and polarizes Th1/Th2 responses improving hosts' survival [77,78,82]; as extreme polarization is detrimental, the "happy valley" hypothesis states optimal host protection at either the Th1- or Th2-peak, where parasites feel "unhappiest" [77]. Though Th2-cells promote partial non-sterile resistance to reinfection, they stimulate disease chronicity due to granulomatous-fibrotic formations mediated by cytokines besides signal transducer and activator of transcription/Stat6 pathways [83]. The role of B-cells is expressed by IgE and IgA immunoglobulins conferring protection with resistance to reinfection [9,84–86]; pre-existing IgE occur in the context of vaccine-induced hypersensitivity [87,88]. IgG4, IgG2 and IgM are associated with susceptibility to reinfection and disease severity, thus antagonists to protective antibodies [9,84–86].

Neonates of infested mothers possess due to foetal exposure or *in utero* priming [14] to transplacentally crossed antigens [17] anti-inflammatory Th2 responses [89], maternal IgG and IgG subclass immunoglobulins, fetal IgM and IgE antibodies indicative of immune system maturation, and proliferated cord blood mononuclear cells (CBMCs) [17,89,90] enabling altered regulated postnatal reactivity and pathology, i.e., lower severity due to smaller granuloma, upon parasite challenge, e.g., sensitization or tolerization [9,46,74,89,91–93]; effects are enhanceable by colostral and breast milk immunoglobulins [17,19,94–96]. Newborns of *S. haematobium* infected Gabonese mothers had anti-ova IgE in their umbilical cord blood reinforcing *in utero* priming [17,97,98]; 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% neonates [101] due to variable maternal infection intensities [18] and offspring's defects in cell-cycle and cell-proliferation/-transcription pathways [16] 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 [17] leads to varying immunoreactivity dependent on the gestational status [89,96,97]. Chemotherapeutic boostering 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), lacks in offspring [18] likely because of sensitization before chemotherapy or impairment by maternal infection intensities, i.e., light infections promote while moderate and high infections prevent sensitization.

3. Treatment and prevention

Globally, nearly 500,000 annual deaths are avertable [2,4,21,104]. The acylated quinoline-pyrazine or praziquantel (PZQ) is the chemotherapeutic in use [53]. PZQ acts poorly against juvenile [105,106] but well against adult schistosomes [6]; disrupting the calcium homeostasis leads to muscle contractions, paralysis [107] and irreversible tegumental changes [14] in permeability and stability visible as blebbing, vacuolation and cytoplasm leakage [14,108]. PZQ's effectiveness is influenced by parasite, e.g., vasculature localization [4,62,63,70,105,109–111], and host factors, e.g., infection intensity [72], immunoreactivity, exposure history, gut microbiota, physiological disposition, and bioavailability. Once administered, IgA, IgE, IgM and IgG1-3 subclass immunoglobulins are detectable inducing approximately 12-months protection against re-infection enhanceable for instance by eosinophils [112], and IgG4 promoting susceptibility to re-infection due to IgE blocking while modulating anaphylactic responses [6,14,113]; regular repeated chemotherapy [50,112] reduces IgG4 titers [111]. Of concern is serious rebound morbidity caused by the re-emergence of missed immature worms upon irregular PZQ administration [41,114–118] seen as saw-tooth phenomenon [119], and evolving resistance [105,120] or reduced sensitivity [22,121]; the latter occurs likely due to genetic variability [122] or maturation of immature not fully eliminated parasite stages exposed to remaining sub-lethal drug concentration [123,124]. Loss of fitness seems tolerable as long as genetic alterations increase flukes' survival to chemotherapeutics [125]. It's standard dose is efficacious against all species though apparently better against *S. japonicum* over *S. mansoni* and *S. haematobium*, and mixed infections [114,126]. PZQ contains equal proportions of biologically active (R-PZQ) and

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inactive (S-PZQ) [127] enantiomers causing half of doses being pharmacologically ineffective [105]. WHO's recommended treatment regimen, administered in a mass drug administration (MDA) [128] or selective at-risk manner [22,129,130], 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 [22,69] as seen for nucleic acid tools detecting trace levels [131] reported subsequent to chemotherapy [131,132] and among apparently healthy individuals [40,133]. Pre-schoolchildren at present unlikely receive PZQ [127] due to paucity of efficacy and safety data [129,131,134]. Schoolchildren in low-risk settings receive PZQ twice during school time or once every three years besides suspected cases [135]; 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 [12,129,135,136].

Prevention includes [137] behavioral changes, health education, improved hygiene and sanitation, environmental and seasonal impacts [138–141], and eliminating freshwater molluscs [2,106,117,140,142–145]. Multi-component approaches [146–148] targeting humans and also animals, i.e., particularly water buffaloes among bovines [149–151] as sources of ongoing transmission [120,152], applied in endemic Asian settings seem promising [150,153–158]. Building on the *S. mansoni* radiation-attenuated cercarial vaccine eliciting shortly post-immunization long-lasting multi-species [159,160] CD4+ Th1/Th2 immunoresponses of >70% [50] emphasizes the necessity to expand prevention by vaccination alone [6,14,161,162] inducing protection against transmission, infection, and disease recurrence [2,142,163] or combined with PZQ, i.e., vaccine-linked therapy [164]. Besides antigenic moieties of e.g. surface membranes, excretory/secretory proteins, tegument, cytosol, and gastrointestinal tract still at the experimental stage [75,165], few candidates advanced to clinical phases, i.e., Sm14 or *S. mansoni* fatty acid-binding protein (FABP), Sm-TSP-2/Sm-TSP-2Al® or *S. mansoni* tetraspanin, Smp80/SchistoShield® or *S. mansoni* large-subunit calpain [50], and Sh28GST/Bilhvax® or *S. haematobium* glutathione S-transferase [58,166–168]; the latter was discontinued lacking efficacy [164]. FABPs take-up, transport and compartmentalize host lipids as schistosomes lack own oxygen-dependent pathways to synthesize long chain fatty acids and cholesterols [169]; homologies in amino acid sequences with e.g. *Echinococcus*, *Clonorchis* and *Fasciola* demonstrate its cross-species multi-purpose vaccine potential [170–173]. TSPs as scaffold proteins are involved in immunoregulatory immunoevasive processes by absorbing host molecules to mask flukes' "non-self" status [174,175]. Phylogenetic polymorphism among protein-protein interacting extracellular mushroom-like loops of TSPs' large domain alters affinity and avidity to host immunoglobulins causing varying protective efficacy [65,176–178]. Calpain as 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 [179]. Calpain is relevant for tegumental biosynthesis and turnover [180] and has species-dependent structural differences in amino acid substitutions [181]. GST regulates e.g. detoxification, antioxidant pathways, fatty acid metabolism, immune modulation, and neutralization of host-derived hydroperoxides [182]. Its crystal structure consists of two similar monomers, each having N- and C-terminal domains; GST of *S. haematobium* and *S. bovis* exceed residue conservation within their domains indicating protective cross-species potential [183]. 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 [42]. 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 [15,149,168,184,185]; aimed for are reductions in worms and egg expulsion by ≥75% [7,8,75] as schistosomes are non-replicating in hosts [5,14,137]. Compatibility with therapeutics and vaccines of national immunization programs is desired [168,184].

4. Transmission models

PubMed, Embase and Web of Science databases were searched for transmission models tackling human schistosomiasis through vaccination; see Table 1 for methodological details and models detected. Initial mathematical modelling is traceable to Bernoulli in the 1760s [186]; Macdonald [48,137,147,187–192] and Barbour [151,187,193–196] developed early schistosomal simulations. Model aims are diverse, e.g., exploring transmission dynamics [197–200], worm mating probabilities [27,201] and programmatic besides operational matters including resource allocation [202–205].

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Predictions derived support e.g. simulating novel hypotheses, designing vaccine trials [199,206–208], implementing interventions [15,186,192,195,209–214] advancing the flukes' control and elimination [106,130,135,143,205,215], and guiding decision- and policymaking [129,198,212,216,217].

AUTHOR(S) Year [Reference]	WOOLHOUSE 1992/1995 [137, 138]	CHAN *et al.* 1996 [143]	CHAN *et al.* 1997 [144]	STYLIANOU *et al.* 2017 [90]	ALSALLAQ *et al.* 2017 [148]	KURA *et al.* 2019/2020 [96, 135]
SCHISTOSOMA 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 aged children/ Total population	Pre-school children aged 1yr and 7yrs	Infants aged 1yr (at-birth strategy)	Total population age-stratified (≤4yrs, 5-14yrs, 15-24yrs and ≥25 yrs)	Total population age-stratified (≤4yrs, 5-14yrs and ≥15yrs)
SETTING	Endemic	Endemic	Endemic	Low, medium, high endemicity	High endemicity	Low, medium, high endemicity
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	30yrs	NA	20yrs and 50yrs	50yrs	30yrs	15yrs
INTERVENTION	• Supplementary and complementary postnatal campaign • 80-90% partial protective vaccine with 10-yr waning efficacy	• Cohort-based pre-school children campaign with/without prior single MDA/PZQ • Age-stratified mass population-based campaign with/without prior single MDA/PZQ • 90% partial protective vaccine with 20-yr waning efficacy	• Vaccine: 25%, 50%, 75% and 99% partial protective product with 80% coverage and 10-yr waning efficacy • MDA/PZQ: 95% instant *per capita* worm reduction and 80% coverage	• Cohort-based infant campaign • Population-based mass campaign • 80% partial protective vaccine with 85% coverage and 50-yr waning efficacy	• Cohort-based infant campaign • Population-based mass campaign • Vaccine: 80% partial protective product with 100% coverage and 10-yr waning efficacy • MDA/PZQ: 75% instant *per capita* worm reduction and 80% coverage	• Cohort-based children campaign with catch-up campaign(s) • Population/Community-based mass campaign with catch-up campaign(s) • Vaccine: varying protective product with high coverage and 5-yr, 10-yr and 20-yr waning efficacy • MDA/PZQ: varying species-dependent instant *per capita* worm reduction and varying age-related coverage
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/≥15yrs 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 peak infection level towards older age due to residual transmission • Protective duration determines optimal age for intervening measures	• ≥60% vaccine efficacy, full coverage and ≥10-yr waning efficacy capable of interrupting transmission in low & moderate transmission settings; immunity & herd immunity build slowly • Higher efficacy, higher coverage and higher protective duration required besides annual boosters in high transmission settings; initial MDA/PZQ presumed beneficial • Vaccine effects equally beneficial disregarding parasite target, i.e., worm survival, female fecundity, worm establishment	• Population campaign: declines in ≤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: 5-24yrs 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 with coverage and frequency augmented and targeted age groups expanded

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

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 December 31, 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*; NA=not available; MDA=mass drug administration; PZQ=praziquantel; WHO=World Health Organization; *vs.*=*versus*

Woolhouse's [218,219] 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 [209]. Limited impact on the cumulative worm burden and increased susceptibility to re-infestation are predicted within a 30-year simulation period [186]; the latter results in rebound morbidity later in life [220] as opportunities acquiring natural immunity gradually and cumulatively [221] through trickle infections [27] are missed following the intervention. Consequently, the age of initial vaccination with boosters throughout life, parasitic targets of protective immunity including magnitude of responsiveness to them [222], and vaccine effectiveness regarding duration, extent and interaction with natural immunity matter [223].

Chan *et al.* [224] apply models, i.e., cohort model targeting pre-schoolchildren *versus* age-structured community-based model [211], to foresee effects of an anti-establishment, anti-fecundity vaccine. Factors presumably impacting vaccine effectiveness relate to targeting naïve and previously or currently infested hosts besides chemotherapy inducing additional antigen release. Though both models show reductions in infection intensities, residual infection and parasite transmission and harboring likely continue [225,226]; vaccinating once at early age inducing long-lived protection or vaccinating repeatedly due to short-lived protection alters parasite transmission impactable further when combined with MDA [224].

Chan and colleagues [227] simulate vaccine impacts on *S. mansoni* infection intensity and longevity of protection, including indirect effects or herd immunity [15], among a random infant and child population, and efforts combining vaccination with targeted or mass chemotherapy. The partial differential density-dependent model [228] encompasses age-dependent parasite exposure [221,229], natural acquired immunity [69,116,228] developing gradually and cumulatively [230,231] with waning upon reduced exposure [221], and vaccine-induced immunity targeting infestation and ova shedding. Vaccine protection reaching 75% lasts 10 years on average; chemotherapy reduces per capita worm burden by 95%; vaccine and drug coverage total 80% each [227]. Simulations reveal pivotal far-reaching reduced infection intensities subsequent to vaccinating the 1-year cohort and indirect effects of diminished transmission among 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

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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 [232] is pivotal to determine the optimal age for interventions [228], e.g., immunizing the youngest leaves them unprotected later in life while immunizing schoolchildren protects them once at highest risk [227]; repeated administration of interventions are required if effects are short-lived [15,115].

Building on classical macro-parasite modeling [137], **Stylianou** *et al.* [112] utilize a simple deterministic concept for assessing partial efficacious vaccine effects on dynamics of *S. mansoni* cercariae and worms [233], i.e., female fecundity and per capita mortality, impacting mating and sexual reproduction, and hosts upon immunization, i.e., 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 [129,133,201,216], density-dependent ova expulsion [234], negative binomial distribution of schistosomes per host, and basic reproductive numbers (R_0) [15,235] of 1.0-1.4, 1.5-2.5 and > 2.5 resembling low, medium and high transmission settings, respectively, are incorporated [112]. Parasite-to-mollusc and parasite-to-vertebrate dynamics require weeks and several years, respectively [236]. Authors delineate that a 60% effective vaccine suffices to interrupt transmission in low and moderate settings while increased effectiveness or multiple annual boosters equivalent to approaches of Anderson *et al.* [237] are needed in high transmission settings, and if protection lasts less than 5-10 years; a vaccine addressing worm establishment and survival besides female fecundity seems equally beneficial. In low transmission settings, ≥18 years are required for breaking parasitic transfer due to slow-building immunity and background mortality lowering the proportion vaccinated that compromises herd immunity; MDA prior to immunization seems most beneficial. Combining human and animal MDA prior to vaccinating humans besides bovines as applied in endemic Asian settings [152,154] appears effective for achieving short- and long-term equilibrium prevalence, i.e., balanced prevalences or R_0 <1, making schistosomal elimination more tangible [120,238].

Alsallaq *et al.* [239] 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 [23,237,240], age-stratified worm burden addressing chances of overdispersion [233], and a partial efficacious vaccine that targets worm accumulation and mortality [240] besides female fecundity with 80% efficacy lasting a decade or beyond two decades when combined with MDA. Vaccination is administered with/without MDA as recurrent childhood campaign among naïve newborns or mass vaccination disregarding current or past parasitic exposure; PZQ kills worms with 75% efficacy within one month. Predictions reveal that mass vaccination and repeated mass or pulse vaccination over age-selective immunization is needed for short- and long-term impacts, respectively [239]; longevity of protection matters similar to findings of Chan *et al.* and Anderson *et al.*. An optimal vaccine should address preferably acquiring cercariae developing to schistosomes besides killing of established worms [163] to interrupt transmission. Combining mass chemotherapy with regular mass vaccination is most beneficial as demonstrated by dramatic declines in incidence rates [186] making schistosomiasis elimination appear more feasible.

Kura *et al.* [129,216] (Figure 1) utilize an individual-based stochastic construct to forecast *S. mansoni* [143,237] among subjects receiving MDA assuming 86.3% efficacy, immunization presuming 100% efficacy, and immunization combined with MDA. The vaccine is given to children ≤5 and ≤15 years in a cohort-based and community-based approach, respectively, including a single or repeated catch-up campaign [216]. Collyer's *et al.* [241] individual-based stochastic model matches Kura's, except it contains 90% vaccine efficacy and 40% adult PZQ coverage. Graham's *et al.* [242] flexible individual-based stochastic framework comprises chemotherapy for diverse transmission settings, and enables adding immunization and molluscicide [147,154,210,226]. Kura's endpoints are WHO's 5% morbidity control and 1% transmission elimination [163] in low-, moderate-, and high-risk sites assessed within 300 simulations over a 15-year period. Disregarding temporary and permanent non-adherers [41,243] due to random real-life like allocation of interventions risks ongoing parasite transmission [133,135]; neglecting current and previous infestations may evoke adverse events [129,216].

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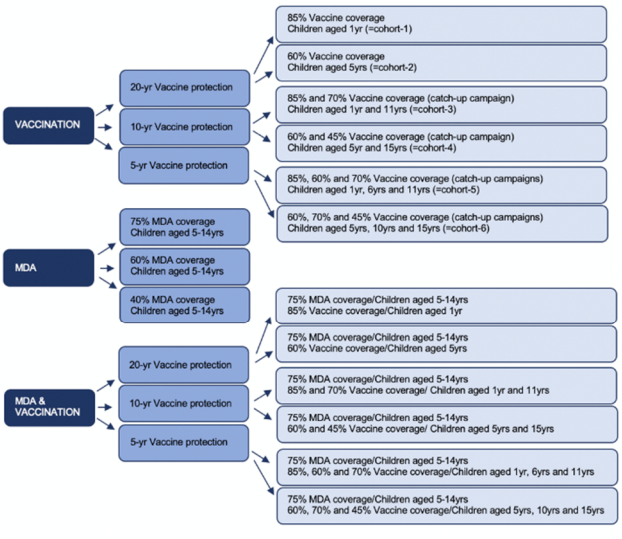

N(a, t)	Total host population
N_v(a, t)	Vaccinated population
N_u(a, t)	Unvaccinated population
a	Host age [year]
t	Time [year]
i	Parasite establishment within host
μ(a)	Host mortality rate
q(a, t)	Population fraction vaccinated
ω	Vaccine decacy rate as 1/duration of protection
β(a)	Effective contact rate leading to parasite survival and growth or *per capita* rate between two subjects per unit time • 0.032 age-specific contact rate or infection rate in hosts aged ≤4yrs • 0.162 age-specific contact rate or infection rate in hosts aged 5-9yrs • 1.000 age-specific contact rate or infection rate in hosts aged 10-15yrs • 0.006 age-specific contact rate or infection rate in hosts aged ≥16yrs
σ	4-6 yrs (5.7 yrs) adult worm life expectancy within host impacting egg production
λ	0.14 fecundity or rate of egg production per female per fecal sample assuming monogamous reproduction and density-dependent fecundity
v1	Worm death rate of 0-1; impact of vaccine on worm death rate of 1
v2	EPG feces rate of 0-1; impact of vaccine on EPG of 0
v3	Age-specific contact rate of 0-1; impact of vaccine on contact rates of 0
M(a,t)	Mean total worm burden in vaccinated and unvaccinated population
M_u	Mean worm burden in unvaccinated population
M_v	Mean worm burden in vaccinated population
Prevalence	School-aged children % egg count threshold >0
Heavy prevalence	School-aged children % egg count threshold >16
L	Environmental concentration of infectious material
ψ	Flow of infectious material into environment/reservoir
F(M(a,t); k)	Egg output in dependence of female fecundity and the mean total worm burden in vaccinated and unvaccinated populations
ρ(a)	• 0.032 environmental relative contribution of infectious stages in hosts aged ≤4yrs • 0.162 environmental relative contribution of infectious stages in hosts aged 5-9yrs • 1.000 environmental relative contribution of infectious stages in hosts aged 10-15yrs • 0.006 environmental relative contribution of infectious stages in hosts aged ≥16yrs
k	Aggregation parameter (non-fixed depending on fluctuations in mean worm burden over time) • 0.04 negative binomial host worm aggregation parameter low-risk setting • 0.24 negative binomial host worm aggregation parameter moderate- and high-risk settings
R_0	Average number of viable reproductive female offspring per female worm (parasite); secondary infectious subjects from infectious subject introduced in totally susceptible population (host) • 1.7 basic reproductive number in low-risk setting with <10% prevalence • 1.8 basic reproductive number in moderate-risk setting with 10-50% prevalence • 3.2-5.0 basic reproductive number in high-risk setting with >50% prevalence
Drug efficacy	86.3% *S. mansoni*; 95% *S. japonicum*; 94.1% *S. haematobium* (Anderson *et al.*, 2015)
Vaccine efficacy	100%

Figure 1. Simplified structure of the *Schistosoma mansoni* individual-based stochastic model

Model based on Kura *et al.* (2015) applying mass drug administration, vaccination, and vaccination combined with mass drug administration (left). Model parameters (right) assuming 300 simulations over 15-year model duration among a presumed human host population $N(a, t)$ of 500 with constant numbers of births and deaths consisting of $N_v(a, t)$ vaccinated population and $N_u(a, t)$ unvaccinated population.

Abbreviations: MDA=mass drug administration; yr=year; yrs=years; EPG=eggs per gram; *S.*=*Schistosoma*

Administering MDA 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 frame presuming 75% coverage [135]. In moderate-risk sites, morbidity is controllable and transmission eliminable, i.e., interruption [132] or true elimination (R_0 <1) [133,237], within 5 (p=0.937) and 15 years (p=0.960) requiring 60% and 75% coverage, respectively. Toor *et al.* foresee elimination within a 10-year span assuming 75% coverage [135]. WHO's endpoints are hardly reachable in high-risk sites also for other species [135,244,245] unless coverage and frequency [246] are increased to 75-85% while including 40% adults [135,143,163,241,247–249]. Coverage needs adjustment to settings' at-risk level [12,129,163,248,249] when combined with other interventions [143,245].

Immunizing 85% 1-year (cohort-1) and 60% 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 when immunizing 85% 1-year and 60% 5-year olds each combined with a catch-up campaign targeting 70% 11-year and 45% 15-year olds, respectively. Vaccinating 85% 1-year and 60% 5-year olds assuming 5-year protection each followed by two catch-up campaigns, i.e., 60% 6-year and 70% 11-year olds (cohort-5) and 70% 10-year and 45% 15-year olds (cohort-6), respectively, 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. 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) [129]. Taken together, while MDA has higher short-term effects on WHO's endpoints [128,248,250], immunization impacts them long-term [135,143,246] since immunity including herd immunity takes time to develop. An optimal immunization strategy to control or even eliminate schistosomiasis depends on a setting's prevalence besides vaccination age, vaccine coverage and longevity of protection [186].

Vaccinating 85% 1-year and 60% 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)

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and 15 years (cohort-1: p=1.000) for controlling morbidity and eliminating transmission, respectivley; 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.* [241] foresee eradication is achievable within 15 years when vaccinating schoolchildren, and treating 75% schoolchildren and 40% adults in a community-based approach [163].

5. Model considerations

Besides conceptual model differences, predictions derived build on vaccines of varying protection and effectiveness 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 facilitating transmission and residual infections though dependent on the at-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 are pivotal, i.e., targeting pre-schoolchildren likely leaves them unprotected later on while targeting schoolchildren probably protects them when at highest risk, including potential boosters throughout life; longevity over magnitude of protection to antigenic schistosomal moieties, i.e., long-lived aiming for single administration *versus* short-lived aiming for repeated administration, is crucial while considering interactions with natural immunity derived also from *in utero* priming and indirect effects or herd immunity. Combining long-term effects of vaccination with short-term effects of chemotherapy [120] as regular repeated vaccine-linked therapy in contrast to a sole intervention seems most promising for achieving WHO's endpoints of transmission elimination and morbidity control.

Referring to vaccine candidates in advanced development [42], i.e., Sm14, Sm-TSP-2/Sm-TSP-2Al®, Smp80/SchistoShield®, and Sh28GST/Bilhvax® [164], reveals that, different to model constructs detected (Table 1), Sm-TSP-2 [251–254], Sm14 [255–257] and Sh28GST [258,259] underwent testing exclusively in healthy adults from non-endemic and Brazilian and Ugandan endemic settings. Sm-TSP-2 Alhydrogel-adjuvanted induced highest IgG titers in non-exposed males and non-pregnant females aged 18-50 years at 4.5 months post immunization with waning six months later [251,252]. Sm14 GLA-SE-adjuvanted administered once intramuscularly followed by two boosters to non-exposed males and non-pregnant females aged 18-49 years lead to augmenting total IgG titers in 88% of subjects through boostering besides IgG1-4 subclasses while lacking IgE expression [255,256]. Sh28GST Alhydrogel-adjuvanted given subcutaneously to non-exposed males aged 18-30 years, including a maximum of two boosters, elicited strong IgG1-3 and IgA, but weak IgG4 and no IgE immunoglobulins [258,259]. Assessments among infested Senegalese children were performed solely for Sm14 [206] pending publication and Sh28GST [207,208], i.e., *S. mansoni* and/or *S. haematobium* infested schoolchildren aged 8-11 years received pre-treatment with one dose PZQ followed by Sm14 GLA-SE-adjuvanted sub-cutaneously including two boosters while *S. haematobium* infected children aged 6-9 years obtained pre-treatment with two doses PZQ subsequent to Sh28GST Alhydrogel-adjuvanted sub-cutaneously including three boosters. Sh28GST was well tolerated during the 38-month follow-up with total IgG, IgG1, IgG2, IgG4 and IgE immunoglobulins detectable and ≥1 recurrence observed among 86.4% and 89.6% of vaccine and control arms, respectively.

Adding short-term effects of PZQ to vaccination tackles schistosomes furthermore [114] seen as 76.7% (r=0.434, p=0.001) to 52-92% cure rate [260], and 86.3% (r=-0.126, p=0.370) egg reduction rate [40,134]. 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 [108], impacted additionally by previous treatment, i.e., best at first over multiply treatment doses [227,261]. Its administration to pre-schoolchildren as crushed tablets and syrup formulations may be considered inducing 87.3% (95%CI 85.7-88.2) and 82.0% (95%CI 72.6-90.0) cure rate, and 97.1%

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(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 [262]. As raised by Anderson *et al.* [133], acquired protective immunity, i.e., widening of antibody spectra with switching from ova-specific IgM and IgG1-2 to larval- and worm-specific IgE [263] in juvenile and adult hosts, respectivley, due to intervening measures [116] and natural exposure [230,264] besides *in utero* priming [9,46,74] need to be considered when making predictions incorporating vaccination to guide decision- and policymaking. Interferences among tegumental and cytosolic antigens [107] released subsequent to PZQ and vaccine antigens is speculated to cause non-specific unwanted immunoresponses [14]; Africans as opposed to Caucasians have more exhausted and activated natural killer cells, differentiated T- and B-cells, and pro-inflammatory monocytes altering immunoprofiles that possess phenotypical and functional heterogeneity due to concomitant infections and genetic diversity [14].

Besides enhancing efforts through vaccination and chemotherapy as multi-component approaches [108], health education in line with socio-cultural and ethnical contexts is capable of impacting human hosts' behavioral attitudes sustainably [133]. 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, including prevention measures, i.e., 32-63% pre-education to 79-96% post-education [265]; consequently, defecation into latrines over free-range and open water sources was practiced more often besides minimizing water contacts [137,246], both associated to lower odds of *schistosomal* infestation [242]. 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 [117]. 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, e.g., construction of water dams, e.g., Senegal and Bafing rivers, Senegal [266], or Yangtze River, China [155], and irrigation channels, e.g., Awash Valley, Ethiopia [267], and forest clearance and agricultural development [268] besides human movement, e.g., seasonal migrant laborers or seminomadic pastoralists [267,269] and large-scale population re-settlements [155], raise concerns of breaking species isolation barriers [270] and deranging dynamics and distributions of schistosomes [133,202,271]; species sympatry and interplay, host switching or spillover through heterogeneous mixing [32], and expansion to new favorable habitats facilitated by altered flukes' vigor [24,270] are likely consequences [270,272]. Regular, prolonged molluscicide beyond the maximum life expectancy of worms [236] utilizing chemical and biological means such as natural predators or competing organisms [108,133,246] also combined with chemotherapy decreases novel infections and re-infections [273–275], e.g., from 12.5-40% to <9% in a *S. mansoni* endemic setting [276], except of insufficient ecological overlap [277]. Notably, Gurarie *et al.* [202,278] 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 [202]. King *et al.* [268] demonstrated *S. haematobium* as the dominant species in Cameroon within 25-30 years subsequent to deforestation and agricultural expansion in the 1960s. Interestingly, human migration between Senegal and Corsica/France for occupational opportunities in food-processing sectors likely re-introduced schistosomiasis to Europe in 2013 despite paucity in understanding the presence of *Bulinus* spp. and *Planorbarius* spp. molluscs [279,280].

6. Conclusions

Modelling predictions aiming to support decision- and policymaking towards schistosomal transmission elimination and morbidity control demonstrate that solely a multi-component approach integrating long-lasting vaccine effects over a single-component approach will be capable of addressing WHO's goals set. A vaccination schedule is pivotal that combines the optimal age for initial immunization, i.e., pre-schoolchildren or schoolchildren, in a cohort-based or population-based manner with existing pre-acquired immunity and longevity of vaccine protection including potential booster doses.

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