

Reduced transmission of human schistosomiasis after restoration of a native river prawn that preys on the snail intermediate host

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Eliminating human parasitic disease often requires interrupting complex transmission pathways. Even when drugs to treat people are available, disease control can be difficult if the parasite can persist in nonhuman hosts. Here, we show that restoration of a natural predator of a parasite's intermediate hosts may enhance drug-based schistosomiasis control. Our study site was the Senegal River Basin, where villagers suffered a massive outbreak and persistent epidemic after the 1986 completion of the Diama Dam. The dam blocked the annual migration of native river prawns (*Macrobrachium vollenhoveni*) that are voracious predators of the snail intermediate hosts for schistosomiasis. We tested schistosomiasis control by reintroduced river prawns in a before-after-control-impact field experiment that tracked parasitism in snails and people at two matched villages after prawns were stocked at one village's river access point. The abundance of infected snails was 80% lower at that village, presumably because prawn predation reduced the abundance and average life span of latently infected snails. As expected from a reduction in infected snails, human schistosomiasis prevalence was $18 \pm 5\%$ lower and egg burden was $50 \pm 8\%$ lower at the prawn-stocking village compared with the control village. In a mathematical model of the system, stocking prawns, coupled with infrequent mass drug treatment, eliminates schistosomiasis from high-transmission sites. We conclude that restoring river prawns could be a novel contribution to controlling, or eliminating, schistosomiasis.

disease | ecology | control | elimination | neglected tropical disease

Multiply just (US) \$0.32, the annual cost to treat a child infected with schistosomiasis (1), by the 114 million children requiring treatment (2), and cheap drug-based treatment can become too costly to sustain. Drug-based control programs for human helminth diseases, termed preventive chemotherapy, have led to spectacular improvements in health and reductions of many worm infections (3). The success has led to new challenges in devising strategies to eliminate these parasites over the long-term, sometimes called the “end game” of infectious disease control (4). For schistosomiasis, this new focus on elimination has sparked a debate over the best strategies to complement drug treatment and interrupt the transmission cycle (5–7). In its May 2012 resolution to eliminate schistosomiasis (World Health Assembly Resolution 65.21) (8), the World Health Assembly called for new procedures to interrupt transmission. Here, we offer evidence that the restoration of a natural predator of the obligate snail hosts of schistosomiasis could be an effective strategy to eliminate disease when performed along with drug treatment. We present the results of a recent pilot program to control schistosomiasis after the construction of the Diama Dam on the Senegal River as an example.

The Diama Dam is only 18 m high, but that is enough to keep the tide from pushing brackish water up the Senegal River. The impounded river is now a stable reservoir of freshwater for people in Dakar and Saint-Louis, Republic of Senegal, and for irrigating surrounding farmland. Unfortunately, just after the dam was built in 1986, an unprecedented, massive, and persistent schistosomiasis epidemic swept through the villages along the river and its tributaries (9, 10). As some had predicted (11), the dam created an ideal freshwater habitat for the snail intermediate hosts of schistosomiasis by reducing flows and saltwater intrusion and increasing algal and plant growth (12). Moreover, the dam extirpated a chief snail predator (13), whose role in the control of schistosomiasis is the focus of our current study.

Schistosomiasis infects an estimated 220–240 million people globally, and 790 million are at risk for infection, more than 90% of whom are in Sub-Saharan Africa (14). Infected humans contaminate water sources with urine or feces containing schistosome eggs that release larvae (miracidia) infectious to snails in the genus *Biomphalaria* (for *Schistosoma mansoni*) or *Bulinus* (for *Schistosoma hematobium*) (Fig. 1). Each infected snail sheds thousands of cercariae, which seek and penetrate human skin. After entering the skin, the parasites migrate to the blood vessels of the intestines (*S. mansoni*) or urinary bladder (*S. hematobium*), where female worms lay 350–2,200 eggs per day (15). Eggs have sharp spines that promote

Significance

Reinfection after treatment is a problem that plagues efforts to control parasites with complex transmission pathways, such as schistosomiasis, which affects at least 220 million people worldwide and requires an obligate snail intermediate host. Our study highlights a potential ecological solution to this global health problem: We show that a species of river prawn indigenous to the west coast of Africa, *Macrobrachium vollenhovenii*, could offer a low-cost, sustainable form of snail control that, when used in synergy with existing drug distribution campaigns, could reduce or locally eliminate the parasite. Biological conservation does not always benefit human health, but our results show that where it does, it could provide a win-win outcome for humans and nature.

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Fig. 1. (A) Adult *M. vollehovenii* prawn. (B) Evidence of prawn predation via characteristic damage on snail shells (arrows). (C) Net enclosure for prawns at Lampsar village.

passage through the tissues across the intestines or the urinary bladder. Nonetheless, many eggs do not complete their passage, lodging in the liver, bladder, or other organs, where they trigger chronic inflammatory processes (16). Death from liver failure or bladder cancer can be preceded by chronic anemia, cognitive impairment in children, growth stunting, infertility, and a higher risk of contracting HIV in women (17, 18). These effects, combined with the poverty of its victims, make schistosomiasis one of the world's most important, but most neglected, human diseases (19). Three decades after the Diama Dam's completion, schistosomiasis is still the chief health concern among the region's rural poor (20).

Our current research was inspired by an experimental study showing persistent and cost-effective schistosomiasis control in Kenyan villages following snail predation by the exotic North American crayfish (*Procambarus clarkii*) (21). Although crayfish are not present in Senegal, a large river prawn, *Macrobrachium vollehovenii* (Fig. 1), is native to the Atlantic coast of Africa and was reported in fishery catches before the construction of the Diama Dam in Senegal (22). River prawns, like crayfish, feed on the snails that transmit schistosomiasis (Fig. 1), and, as reported in laboratory experiments, captive prawns can control snail abundance (23).

Ecological theory supports the idea that the river prawn can eliminate the parasite. The prawn acts as an "intraguild predator" of the schistosome because it both preys on the larval worm when eating infected snails and competes with it by eating the parasite's host. An intraguild predator can extirpate an intraguild prey, such as the schistosome, when the intraguild predator, like the river prawn, is a generalist and its competitor prey, the larval schistosome, is a specialist (24).

The natural history of the region also supports the hypothesis that river prawns can control snails. Before the dam, when river prawns were more common, human schistosomiasis prevalence was low (25). The Diama Dam impeded the annual downstream female migration to the estuary and blocked the upstream return of larvae, after which the river prawn fishery collapsed (13, 23). Prawn extirpation upriver of the dam was concurrent with a dramatic escalation in the prevalence and intensity of human schistosomiasis in the Lower Senegal River Basin (9, 10). It is plausible that the consequent release of snail populations from predation contributed to

snail population expansion and to the schistosomiasis epidemic. If so, restoring prawn populations could reduce snail populations and help curb schistosomiasis transmission. Moreover, this hypothesis raises three questions: (i) Can prawns reduce snail abundance at a village water-contact site as they do in aquaria, (ii) can snail population reduction by prawns control schistosomiasis in humans, and (iii) how might the combination of prawn stocking and chemotherapy affect snail populations and parasite elimination?

We addressed these questions with the combination of a field experiment and a mathematical model (*Materials and Methods*). Logistical constraints limited our field experiment to a single control and experimental village (we discuss the limitations imposed by lack of replication below). Briefly, after recruiting two similar villages upriver of the dam, screening participants for schistosomiasis, and confirming (through trapping) that prawns were scarce in nature (13), we stocked prawns at the downstream village in the pair into a 10-m \times 20-m net that enclosed an opening in the reeds along the shoreline that villagers used to access the river (Fig. 1). The other village was a control site without prawns. Then, we tracked snail infection prevalence and abundance at these two sites over 18 mo after adding prawns. Unfortunately, there were no comparable snail data collected before the prawn intervention. After treating the village residents enrolled in the study at both intervention and control sites with the anthelmintic praziquantel in three follow-up visits, we measured schistosomiasis reinfection rates. Finally, we created a mathematical model, parameterized with independent data derived from the literature, as well as published and unpublished laboratory data, to simulate the effect of prawn stocking on schistosome transmission dynamics and to compare model outcomes with those outcomes observed in the field.

Results

Prawn Enclosure Experiment. Snails were less abundant in the prawn enclosure after prawns were added (intervention village) than at the control village without prawns (Fig. 2). There were \sim 50% fewer *Bulinus* spp. snails at the village where we added prawns compared with the control village (mixed effects Poisson regression with time as a random effect, $P < 0.0001$). More importantly from a human health risk perspective, there were \sim 80% fewer schistosome-infected (shedding) *Bulinus* spp. snails (mixed effects Poisson regression

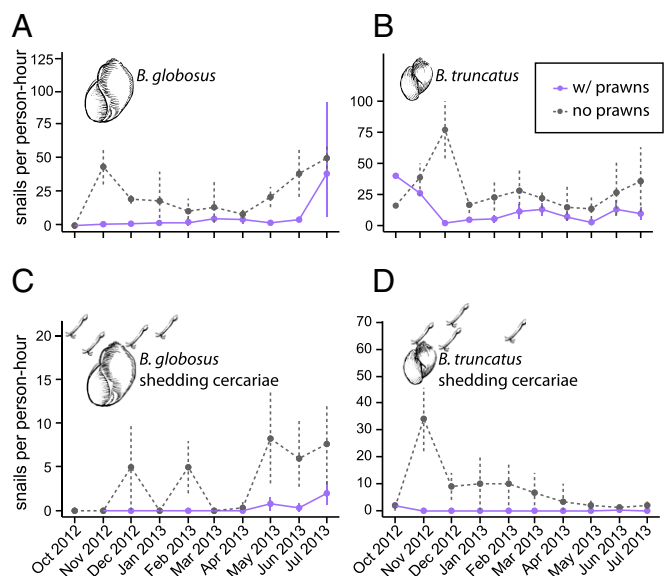


Fig. 2. Relative density of snails after prawns were installed at the intervention site (w/prawns) and control site (no prawns) from October 2012 to July 2013; (A) total *Bulinus globosus*, (B) total *Bulinus truncatus*, (C) *B. globosus* shedding schistosome cercariae, and (D) *B. truncatus* shedding schistosome cercariae.

Table 1. *S. hematobium* prevalence and infection intensity among study participants

Site type	Variable	Baseline	18 mo	Change, %
Intervention (prawn) site	Prevalence	64%	58%	-9
	Heavy infection (>50 eggs per 10 mL)	11%	6%	-46
	Eggs/10 mL urine (AM)	31.9	10.2	-68
	Eggs/10 mL urine (GM)	3.27	2.9	-11.3
	Control site	Prevalence	30%	78%
Control site	Heavy infection (>50 eggs per 10 mL)	4%	12%	+200
	Eggs/10 mL urine (AM)	6.5	18.3	+181
	Eggs/10 mL urine (GM)	0.86	6.1	+616

AM, arithmetic mean; GM, geometric mean.

with time as a random effect, $P = 0.0001$). The results were similar for both *Bulinus globosus* and *Bulinus truncatus*.

Praziquantel treatment, especially when given in two consecutive doses a few weeks apart, results in high cure rates and egg reduction rates for schistosome parasites (26). Thus, treatment presumably cured many participants, after which some were reinfected. Although the village where we added prawns started out with a significantly higher schistosome prevalence (proportion of individuals infected) in humans [before prawns, odds ratio (OR) intervention/control = 5.2, 95% confidence interval (CI): 2.2–12.2], reinfection prevalence was lower than in the control village after prawns were stocked (OR intervention/control = 0.27, 95% CI: 0.12–0.60; Table 1). Results were similar for heavy infections (Table 1), defined for *S. hematobium* as >50 eggs per 10 mL of urine, with a lower prevalence of heavy reinfection among people living at the prawn site during all follow-up visits (OR intervention/control = 0.22, 95% CI: 0.08–0.61). The statistical difference in reinfection prevalence between the villages is best shown as a significant interaction between village and time in the before-after-control-impact (BACI) analysis ($P < 0.0001$). Even more important are the results for our proxy of infection intensity (number of eggs in the urine; Fig. 3 and Table 1), which is the best predictor of human disease (27). That is, despite having an initially higher egg burden before adding prawns, villagers had significantly lower egg burdens after we stocked prawns compared with controls at all follow-up time points (BACI interaction term, $P < 0.0001$; Fig. 3). These results, although not proof of a prawn effect per se, are consistent with the hypothesis that prawns, by reducing snail abundance, can reduce reinfection rates in humans.

Mathematical Model. The mathematical model revealed three categorical outcomes resulting from increasing prawn stocking density, consistent with models of generalist intraguild predation (24): (i) reduced disease in humans with increasing prawn density, (ii) parasite extirpation from the snail population, and (iii) snail extirpation. These states switch at specific prawn densities. At low prawn densities (as in the field experiment), each added prawn reduces infected snail density through intraguild predation on schistosomes (Fig. 4). The decline in infected snail density leads to a similar decline in the worm burdens in humans (Fig. 4B) even though the infection prevalence in humans declines little (Fig. 4A and C), just as we observed in the field. Above 0.3 prawns per square meter (range: 0.16–0.9; Fig. S1), intraguild predation eliminates the parasite from the snail population because prawns eat newly infected snails before they can shed infective cercariae. Ironically, the decline in human egg burdens releases uninfected snails from parasitic castration; therefore, although the abundance of infected snails decreases, the number of susceptible snails may increase, peak, and then decrease at increasing prawn densities. A second critical threshold in prawn density, 0.6 prawns per square meter (range: 0.25–2.0) exists above which prawns locally extirpate the snail population in the model (Fig. S1), much as in laboratory

experiments, where prawns cause recruitment failure in the snail population (23).

Prawns are able to persist in the system after extirpating snails because they can switch to other foods as snails become rare. The gap between the first and second critical densities widens as the prawn-free R_0 , defined here as the expected number of adult parasites generated per adult parasite (p. 138 in ref. 28), or attack rate of prawns toward snails decreases (Figs. S2 and S3). In every scenario, prawns have their strongest effect on infected snail density, and fewer infected snails translates to a lower parasite burden in villagers.

The parameterized model (Table S1) found a good fit between observed and predicted differences in disease prevalence (-18% vs. -24%, respectively) and egg burden (-50% vs. -57%, respectively) in villagers at the intervention and control villages (Table S2). By including seasonality in snail population growth, the model was further able to reproduce the seasonal reinfection patterns observed in the field (Fig. S4).

The correspondence between field patterns and model predictions gave us the confidence to use the model to explore hypothetical control scenarios. Specifically, we were interested in comparing the control achieved by mass drug administration (MDA) of praziquantel, by prawn stocking, or by a combination of both. Modeling MDA by itself (Fig. 5A and D) first reduces human prevalence and worm burden in the treated population (i.e., those individuals who received praziquantel, which was 80% of the total population in this simulation) and then slowly reduces infection in the untreated population. However, in this high-transmission scenario, without continual MDA treatment, prevalence and worm burden return to baseline levels within 5–10 y. In the prawns-only example, prawns maintained at 0.25 per square meter (Fig. 5B and E) can eradicate schistosomiasis without MDA, but only after stocking prawns for 20 y. In contrast to prawns or MDA alone, the integration of prawn stocking with MDA leads to a rapid decline in disease (<5 y) and local extirpation of the parasite from the snails (Fig. 5C and F).

Discussion

Adding prawns to a village water contact area was associated with a subsequent decline in snail densities and reduced schistosomiasis transmission. Although the trajectories of the two villages are consistent with a prawn stocking effect, unseen differences between the villages could have led to changes in snail populations and reinfection, including changes in snail habitat, human behavior, or outside medical care, or it is possible that the prawn enclosure reduced snail abundance for reasons other than

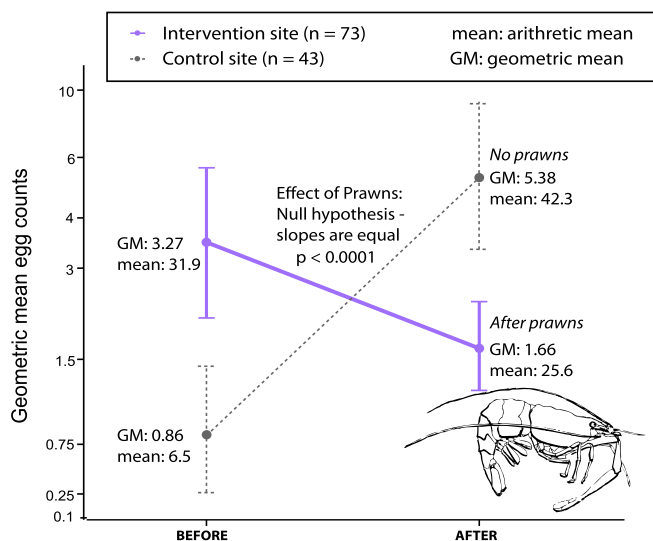


Fig. 3. BACI of prawns on the intensity of *S. hematobium* infection (GM egg burdens) among participants at the intervention and control sites.

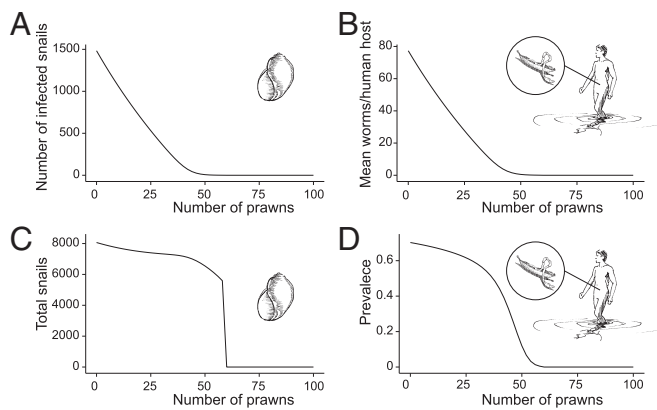


Fig. 4. Effect of prawn density on number of shedding snails (A), human worm burden (B), total snail population (C), and human infection prevalence (D) in response to an average density of prawns ranging from 0 to 100 prawns per 200 m².

prawn stocking. Despite these alternative explanations, the results of the prawn stocking experiment in Senegal were consistent with (i) laboratory experiments showing that river prawns can control snail populations (23), (ii) Kenyan field experiments showing that crayfish reduce snail populations and human reinfection (21), and (iii) the predictions of our simple mechanistic model of schistosomiasis transmission. For these reasons, and assuming that our study villages are characteristic of the region, restoring *M. vollehovienii* prawns to the Senegal River system could benefit villagers now subject to chronic schistosomiasis. The model indicates that health benefits would increase with prawn stocking density and that high stocking density has the potential to achieve local disease elimination, especially along with medical intervention, such as MDA.

Although the net pens at the intervention village encompassed the area used by villagers for their daily water needs, participants were in contact with water outside the “prawn-protected” area. For example, most families were in contact with the water at nearby garden plots or rice farming allotments, or while fishing or working in the commercial rice or sugar cane fields (Table S3). This observation helps explain the moderate effect of prawns on human reinfection. Disease control should benefit from a broader distribution of prawns than our net pens allowed.

Wide fluctuations in reinfection rates across seasons were evident, leading to synchronized patterns of reinfection at the intervention and control villages, with some seasons (primarily the rainy season) having high reinfection at both sites (SI Text).

This seasonality in reinfection highlights the importance of timing when considering MDA or prawn-stocking interventions.

There were also limits to our manipulation. For instance, transport stress reduced prawn survival, and monitoring of the enclosure over time suggested that the realized prawn density, ~0.125 prawns per square meter, was one-half to one-quarter of the density required to eradicate infected snails locally in the model. Furthermore, our enclosure was not impervious to immigration by infected snails or cercariae, and snails might have more refuges in the river environment than in aquaria. A more extensive prawn enclosure, with higher stocking densities, would likely have greater public health benefits than seen in our experiment.

An obvious question is how to restore river prawns. One way is to build a prawn passage (ladder) into the Diama Dam. If successful, a prawn passage could replenish natural recruitment and migration, thus restoring prawns to the upper reaches of the river, where they are now excluded. It is important to note that natural prawn densities found in undisturbed ecosystems approach (29, 30)—and the prawn densities in *Macrobrachium* aquaculture (31) exceed—the critical threshold required for local disease elimination predicted by the model. For this reason, aquaculture, if made cost-effective, could make it easier for native river prawns to reduce schistosomiasis and might also boost the economic benefits of restoring prawn fisheries.

One might worry that harvesting prawns would lead to a trade-off between profits and disease control. Fortunately, because small, fast-growing prawns offer the highest snail-killing efficiency per gram (23), large prawns can be harvested for food or sale without affecting snail control, so long as prawn densities are maintained through natural recruitment (now blocked by the dam) or restocking via aquaculture. In fact, small prawns might do better in the absence of large prawns because of cannibalism (32). Therefore, we hypothesize that scaling up river prawn restoration and aquaculture and optimizing its economic benefits could provide a needed, affordable, and sustainable tool to complement drug distribution campaigns, and perhaps even eliminate schistosomiasis in the Senegal River Basin, while offering nutritional protein and marketable goods for local populations.

Schistosomiasis epidemics often follow dam projects (14). There are many river prawn species around the world (33), and their restoration to dammed areas could also reduce schistosomiasis. In other countries, like Kenya, exotic crayfish have become naturalized and might provide health benefits if fostered near transmission sites. Moreover, other parasitic diseases transmitted by snails may also be controlled by prawn restoration. For example, cattle and sheep trematodes cause economic losses and contribute to food insecurity in Africa (34). Many of these trematodes are transmitted by snails that share similar habitats and morphology with those snails carrying human schistosomes. As generalist feeders and prey for top predators,

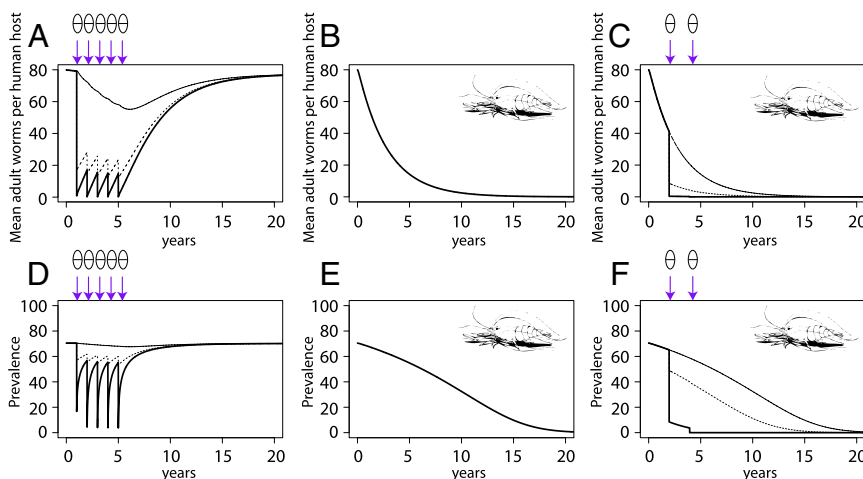


Fig. 5. Trajectory of human schistosomiasis worm burdens and prevalence in a local population of 1,000 individuals under three control scenarios: MDA using praziquantel alone yearly for 5 y with 80% coverage (A and D), prawns maintained at a density of 0.25 per square meter for 20 y (B and E), or prawns maintained at a density of 0.25 per square meter and MDA applied in years 2 and 4 only (C and F). Thick, solid lines indicate the treated population (those participants who received praziquantel); thin, solid lines indicate the untreated population (those participants who did not receive praziquantel); and dashed lines indicate the mean population (including treated and untreated individuals). Arrows show the timing of MDA.

Table 2. Human subject (participant) characteristics at the experimental (prawn stocking) and control sites

Site characteristic	Intervention (prawn) site	Control site
Median age (range)	11 (4–50)	11 (4–51)
Female/male ratio	1:1.2	1:1.8
Sample size (no. recruited at baseline)	176	129

prawns could have many additional unanticipated effects. Overall, we suspect that these effects would help restore the Senegal River food web to its preexisting state before the construction of the Diama Dam.

Where drugs alone fail to control schistosomiasis due to rapid reinfection, prawns may offer a complementary strategy. In some endemic settings, reinfection is rapid because people lacking alternatives are soon reexposed to snail- and parasite-infested water. Neither the worm nor the treatment triggers a long-lasting immune response; therefore, drug treatment, without addressing environmental exposures, offers a temporary solution at best. Eliminating transmission of schistosomiasis, as called for by World Health Assembly Resolution 65.21 (8), seems unlikely without a more sustainable approach. The synergy between drug treatment and snail predators shown here suggests that with a combined strategy, schistosomiasis might be locally eliminated in endemic areas. The next steps include replicating this study to improve confidence in the results, formally assess economic benefits, and evaluate options for prawn restoration in the Senegal River Basin.

Biological conservation does not always benefit human health, but where it does, it provides a win-win outcome for humans and nature (35). Add the economic benefit of aquaculture to the equation, and river prawn restoration might become a win-win-win: for disease control, biodiversity restoration, poverty alleviation, and improved nutrition.

Materials and Methods

Ethical Statement. The Human Research Ethics Committee of the Senegalese Ministry of Health reviewed and approved the study protocols. After obtaining informed consent, schistosome prevalence and parasite infection intensities were quantified among human study participants using standard protocols: urine filtration for *S. hematobium* (36) and the Kato–Katz thick smear for *S. mansoni* (37).

Epidemiological and Ecological Field Data Collection. We surveyed villages in June 2011 before adding prawns. The two matched villages recruited to this study were situated 0.4 km apart on the Lampsar River in the Lower Senegal River Basin. The water access sites were well defined, and thick reeds (*Typha* sp.) impeded all other nearby water access. Population size was ca. 1,000 and 300 in the intervention and control villages, respectively. Participant characteristics were comparable between the two matched sites (Table 2). Human schistosomiasis was measured as infection prevalence (proportion of people with eggs present in the urine), mean egg burden (arithmetic mean of the number of eggs per 10-mL urine sample), or geometric mean (GM) egg “intensity” among participants. The following GM formula was used [also known as the “Williams mean” (38)]: $GM = (\text{egg count} + 1) - 1$, to allow for inclusion of participants with no eggs, which is consistent with previous literature (39). Before stocking prawns, both villages had high *S. hematobium* infection rates (Table 1), but few *S. mansoni* eggs were detected: Four of 161 patients evaluated (2.5%) had low-level *S. mansoni* infection at baseline, and none passed any *S. mansoni* eggs at the first follow-up. Thus, only *S. hematobium* infections were further analyzed for this study.

In December 2011, a three-sided net enclosure, ca. 20 m wide by 10 m long, was constructed around the naturally defined perimeter at one village’s water contact site; the enclosure’s fourth side was the beach at which villagers access the water (Fig. 1). The net was constructed of durable nylon with a mesh size of 1 cm. It was attached to vertical metal poles and secured at the bottom by sand bags. In January 2012, wild river prawns were collected from the Lobe River in Cameroon (Gulf Aquatics, owned by Cyrille Dening Touokong, Douala, Cameroon), shipped by airfreight, and trucked to

the village. Prawn stocking was repeated every 5–7 mo (July and November) in 2012 and bimonthly in 2013.

We monitored snail density and schistosome prevalence in snails at the intervention and control sites after prawns were stocked at the intervention village. Two trained technicians sampled snails biweekly from October 2012 to September 2013, by searching for 1.5 min with standardized snail scoops at 10 equally spaced points along the site edges (40). Those snails susceptible to schistosome infection (*Biomphalaria pfeifferi*, *B. globosus*, and *B. truncatus*) were put in jars filled with river water and returned to the laboratory. By midday, all snails were cleaned in distilled water and placed under bright artificial light for 30 min. Those snails shedding cercariae, with morphologies consistent with *Schistosoma* spp., were recorded as infected. Those snails not shedding cercariae or those snails shedding cercariae not consistent with *Schistosoma* spp. morphology were recorded as uninfected.

In February–March 2012, 7 mo after baseline testing, all study participants received praziquantel, regardless of infection status, at a dose of 40 mg/kg, based on a standard dose pole (41). The same praziquantel dose was given again 3 wk later in a double-dose protocol designed to treat both adult and juvenile worm infections for enhanced cure rates (26). Participants were then advised to go about business as usual. Participants were next surveyed in July 2012, February 2013, and September 2013. At each follow-up, participants were tested for *Schistosoma* eggs in urine or feces, and those participants who were positive were offered treatment as a single 40-mg/kg praziquantel dose.

We compared schistosomiasis prevalence and intensity in study participants living at the intervention and control villages before and after prawns were installed at the intervention village. Statistically, this comparison was achieved by testing for an interaction effect (BACI interaction) between the control/intervention and before/after groups within a generalized linear mixed model, including individual patient identification and testing date as random effects to account for repeated measures at multiple time points (Fig. 3). A binomial error distribution was used for human schistosomiasis prevalence (infected/uninfected), and a negative binomial error distribution was used for egg intensity data. The statistical tests also controlled for several covariates: subject age, gender, and their interaction. As an unreplicated comparison, the statistical tests evaluated whether the villages were significantly different, and not whether there was a significant prawn effect per se (which would have required a substantial replication of villages far beyond the means of this study).

Schistosomiasis Model That Includes Predation on Intermediate Host Snails.

Building on classic models (42–45), we extended the models by including snail population dynamics and logistic population growth, with parasite infections partially to fully castrating snails (46, 47), as well as a managed snail-predator population.

Disease dynamics in snails followed a compartmental susceptible-exposed-infected framework, whereas human infections tracked intensity as mean worm burden (43). The model tracked infection dynamics among snails and humans at a single site (we assumed no immigration), with a spatial scale consistent with a homogeneous mixing assumption (e.g., scale of the 20-m × 10-m prawn enclosure). The basic model had the following four differential equations:

$$\frac{dS}{dt} = f(1 - \varphi N)(S + zE) - \mu S - \frac{qPE}{1 + qNT_h} - \beta\omega\eta Mh, \quad [1]$$

$$\frac{dE}{dt} = \beta\omega\eta Mh - \mu E - \frac{qPE}{1 + qNT_h} - \sigma E, \quad [2]$$

$$\frac{dI}{dt} = \sigma E - (\mu + \alpha)I - \frac{qPI}{1 + qNT_h}, \quad [3]$$

$$\frac{dM}{dt} = \lambda I - (\nu + d)M, \quad [4]$$

with *S*, *E*, and *I* being susceptible, exposed, and infectious snail classes, respectively, and with *N* being snail density and *M* being the mean parasite burden among human hosts. The model was parameterized using data from the literature and published and unpublished laboratory studies performed previously by the authors (SI Text).

The model simulations were run in R, version 3.0.2 (48), using the DeSolve package to calculate numerical solutions to the system of ordinary differential equations. Equilibrium solutions were achieved by running simulations for 30 y in daily time steps. Mass drug treatments, with or without prawns, were simulated by applying a pulse function that reduced the treated population’s mean parasite burden by 99% [a plausible, if not optimistic, level of drug efficacy consistent with other field studies (49, 50)].

We assessed whether the model could qualitatively replicate the observed patterns of reinfection in the human population at the control and experimental sites (SI Text). Because Eqs. 1–4 could not reproduce the seasonal variation in reinfection patterns, we extended the model by allowing snail reproductive rate, f , to vary as a sine function, $f(t)$, with peak reproduction in February through May. The seasonal model was able to reproduce the fluctuating reinfection patterns at the three follow-up visits in the field trial (SI Text).

After assessing equilibrium solutions and the model's qualitative fit with field data, we used the model to explore a set of hypothetical scenarios for disease control and elimination: (i) yearly MDA at 80% coverage, applied for 5 y; (ii) prawn stocking (indefinitely) at a constant density of 0.25 per square meter; and (iii) prawn density at 0.25 per square meter and MDA applied twice, 2 y apart (with the same 80% coverage as in the first scenario). We

then plotted the resultant trajectories of human worm burdens and infection prevalence for 20 y (Fig. 5).

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Supporting Information

Sokolow et al. 10.1073/pnas.1502651112

SI Text

Model Parameterization and Sensitivity to Model Parameters, Calculating Critical Prawn-Density Thresholds Given Variations in Parameter Values. Predation was modeled with a Holling type II saturating functional response parameterized from laboratory data (1), with q being the attack rate and T_h the handling time parameter. The mean prawn density in the intervention site, P , was modeled as a constant parameter that varied from zero to several hundred prawns per site, which considers the predators as a constant managed population controlled by both stocking rates and the survival of prawns after stocking (i.e., P represents the realized, average prawn density at a site). Additional parameter explanations, estimates, and references can be found in Table S1.

We assessed whether the model could qualitatively replicate the observed patterns of reinfection in the human population at the control and experimental sites. To this end, the model assumed that 100 people were treated at each site, out of a total population of ca. 2,000 [i.e., 10% mass drug administration (MDA) coverage], which is similar to field conditions. At baseline, the model simulated a double-dose MDA, administered 3 wk apart, as in the field study. In addition, the model simulated prawn stocking in the experimental site by setting prawn density to ca. 25 prawns per enclosure, or 0.125 per square meter (which is the estimated average realized prawn density within the experimental enclosure calculated from the starting stocking densities and estimated prawn survival rates based on trapping data).

We used the model to assess uncertainty regarding the prawn densities needed for disease elimination or local snail population extirpation. To this end, we randomly varied each parameter using a normal distribution and a 10% coefficient of variation, with the following exceptions:

- i) The attack rate at low density, q , was varied by one order of magnitude below the laboratory-derived value up to the laboratory-derived value (random uniform variation) because we considered the laboratory-derived value as an upper bound, given that factors present in the natural situation were likely to reduce predation efficiency (e.g., habitat complexity, refuges, reduced visibility) compared with predation efficiency measured in laboratory aquaria.
- ii) The handling time, T_h , was varied as a random normal variable with mean and SD both estimated by empirical laboratory studies in the study by Sokolow et al. (1).
- iii) The dispersion parameter of the negative binomial distribution, k , was varied from empirically derived minimum and maximum values estimated from Senegalese patient field data [collected in this study for *S. hematobium* and in the study by Webster et al. (2), for *S. mansoni*], and k was randomly uniform along that range.
- iv) Human life expectancy was left at a constant 60 y and was not varied.

We assembled 100 parameter combinations using the random procedures described above. For each parameter combination, we simulated the system with varying numbers of prawns ranging from 1 to 500 prawns per 200 m² (0.005–2.5 prawns per square meter) and estimated the equilibrium number of susceptible, exposed, and infected snails. The minimum prawn density required for quasi-extinction (less than one snail remaining) at equilibrium for infected snails (disease elimination) or all snails (local snail extirpation) was recorded.

The randomly assembled parameter combinations resulted in a range of values of the prawn-free R_0 from 1.7 to 7, which is consistent with the range of published estimates (3, 4). The resultant median and range of prawn densities required for disease elimination or local snail extirpation are shown in Fig. S1. For each individual simulation, we also calculated the ratio of prawn densities required for disease elimination vs. local snail extirpation, and we plotted these ratios in Fig. S2. The results show that as prawn-free R_0 increases, the ratio between the two critical prawn-density thresholds also increases (linearly) approaching 1, meaning that the critical densities for disease elimination approach the critical densities for local snail eradication. On the other hand, as R_0 is reduced, this ratio decreases toward zero, meaning that disease elimination may occur at much lower prawn densities than required for local snail population extirpation. Similarly, as the attack rate of prawns on snails is reduced, the ratio of the two critical densities decreases (Figs. S2 and S3). Thus, for most cases, local snail extirpation is unlikely at the prawn densities required for disease elimination.

Reinfection Rates and Seasonality. Studies from various regions across Africa have suggested seasonality in human schistosome transmission, usually inferred from snail population data, cercarial output measurements, or rodent sentinel studies (5–10). Only a few studies have demonstrated seasonality in transmission and reinfection rates in the natural definitive (human) host. There were three human reinfection periods tracked during this study (Fig. S4).

The first reinfection period occurred over the course of 5 mo after a double-dose praziquantel treatment (40 mg/kg per dose, with two doses 3 wk apart) in February 2012. During this period, which coincided with the dry season, the reinfection rate was very slow at both the treatment and control sites.

The second reinfection period occurred over 7 mo (July to January) after all patients found to be positive for schistosome infection were treated with a single dose of praziquantel (40 mg/kg) in July. In contrast to the first reinfection period studied, this second reinfection period showed markedly high reinfection rates at both the treatment and control sites. A large portion of this second reinfection period occurred over the rainy season (which lasts from June to October), suggesting that the rainy season and/or the period just before or after the rains may have higher transmission rates than the dry season (which lasts from November to May).

The third reinfection period occurred over 6 mo after positive patients detected at the second follow-up were again treated with a single dose of praziquantel in February (40 mg/kg). The reinfection rate during the third reinfection period was intermediate to the reinfection rate found at the first and second reinfection periods, and, indeed, the third period was of intermediate length (6 mo instead of 5 or 7 mo) and occurred partly in the dry season and partly in the rainy season.

Taken together, these data suggest that reinfection rates are rapid in this region, requiring just a few months to rebound to very high prevalence, and that the rainy season months from June to October may pose a higher human reinfection risk than the dry season months of November to May, similar to results reported by Webster et al. (2), which tracked reinfection in an *S. mansoni* hotspot in a nearby village in northern Senegal.

In Mozambique, *S. hematobium* human reinfection rates after praziquantel treatment were shown to be lower during the cool, dry season, although patients were followed for only 2 mo after

treatment (11). Likewise in South Africa, human reinfection with *S. haematobium* was highest during the warm/wet months and lowest during the cool/dry months (12). In a relatively small study in Nigeria, where warm temperature and rainfall occur in opposite rather than overlapping seasons, the highest transmission rate was seen in the warm/dry season rather than the cool/rainy season (13), suggesting the effects of temperature on transmission may be dominant over the effects of rainfall. Other variables besides snail population growth that might change seasonally to influence reinfection risk include egg survival time outside the host (presumably higher in higher

humidity) and the rate of egg passage into the surface freshwaters (presumably higher with more runoff), as well as seasonal differences in human behavior [e.g., the rainy season and the months just before and just after it are the hottest months in the region and may promote more water contact, as has been shown in other areas (14)].

Studies to investigate further the factors involved in the observed, marked differences in transmission of human schistosomiasis across seasons could help to plan the timing of yearly praziquantel administration and/or prawn reintroduction campaigns to maximize their benefits (15).

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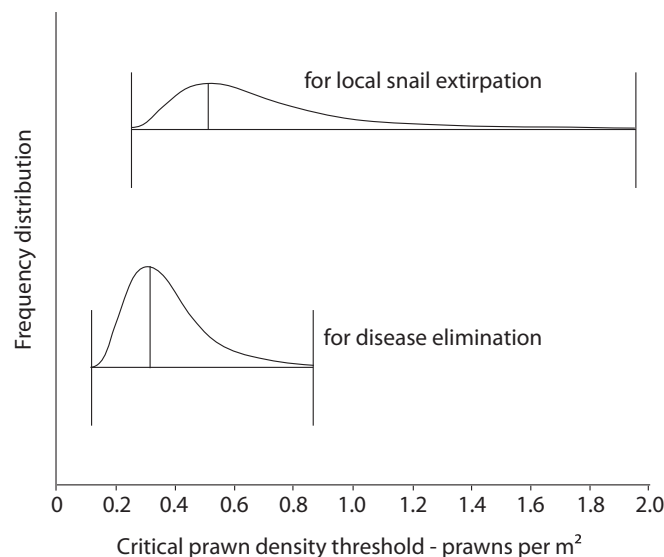


Fig. 51. Frequency distributions for the critical prawn density for snail extirpation (Top) and disease elimination (Bottom).

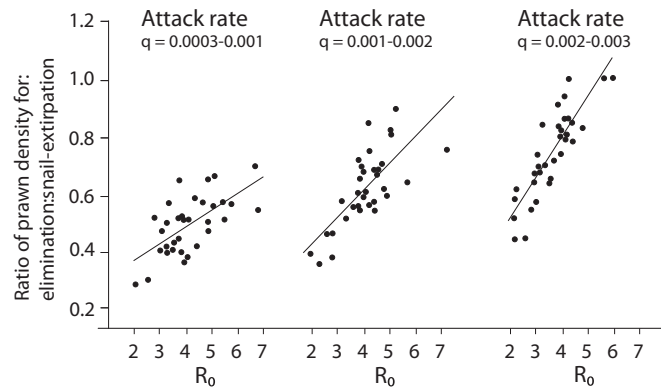


Fig. 52. Relationship between the prawn-free R_0 , defined here as the expected number of adult parasites generated per adult parasite, and the ratio of the first and second critical prawn densities (i.e., critical prawn density for disease elimination and snail extirpation, respectively) across varying attack rates (q).

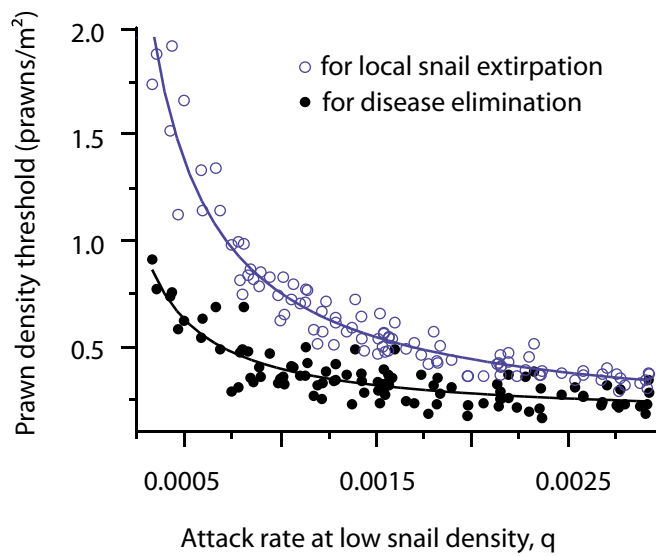


Fig. 53. Relationship between the attack rate (q) and the critical prawn densities for disease elimination and snail extirpation.

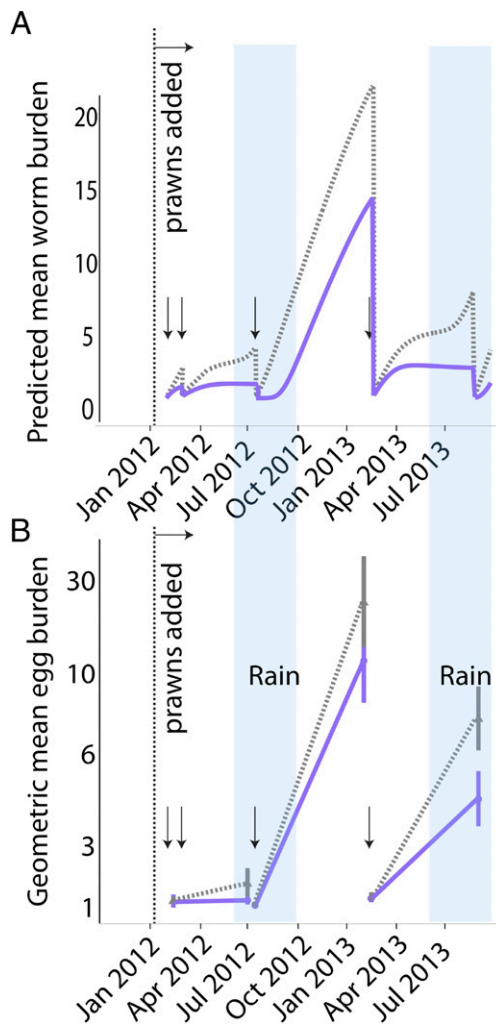


Fig. S4. Seasonal reinfection patterns. (A) Reinfection patterns in predicted mean worm burden per capita, based on the schistosome transmission model. (B) Actual GM egg burdens at each of three follow-up time periods during the Project Crevette field study (note that GM egg burdens are represented on a log scale). Blue-shaded regions show the timing of the rainy season. Solid lines indicate prawn site, and dashed lines indicate control site. Vertical arrows indicate praziquantel administration to both study populations (intervention and control). The differences between the disease burdens at the prawn vs. control site at each follow-up time point, July 2012 (5 mo), February 2013 (12 mo), and September 2013 (18 mo), are shown in Table S2.

Table S1. Explanation of parameters

Symbol	Explanation	Starting value	Source
P	Prawn density/site (assumed constant, based on periodic stocking)	0–500	Our unpublished data on stocking effort and estimates of prawn mortality
H	Initial human population abundance per site	1,000	Our unpublished data on population size at various villages
f	Instantaneous intrinsic fertility rate of snails including survival to detectability (>5.5 mm)	0.16 per day	(1)
φ	Density-dependent parameter for snail population growth (roughly the inverse of carrying capacity per site)	$\sim 1/10,000$	Equivalent to ~ 50 snails per square meter on average (1)
β	Per capita snail infection probability	$4 * 10^{-6}$	No data available, calibrated to match expected R_0 of 1–7
rF	Total number of reproductive females (a variable function of M , which is the average number of adult worms per human host)	$0.5 * M * H$	In the simplest case (assuming 1:1 gender ratio and $M * H \gg 1$)
M	Miracidial shedding rate per reproductive female divided by miracidia mortality	0.8	Little data available, calibrated to match expected behavior of the system
Q	Per capita attack rate of prawns on snails per site at low snail density [scale-dependent, adjusted for size of site ($\sim 200 \text{ m}^2$)]	0.003	Laboratory-derived data (2)
T_h	Prawn handling time parameter (<i>sensu</i> Holling's disk equation), essentially the inverse of maximum number of snails consumed per prawn per day	0.1	Our laboratory data (2); T_h is the inverse of the sustained daily average consumption of snails by adult prawns: (average, 7.9 ± 1.2 ; range, 2–20 snails per prawn per day)
Z	Fraction of exposed snails that reproduce	0.5	(3)
M	Natural mortality rate of uninfected (or exposed) snails	1 per 50 d	(4)
Σ	Rate of conversion from exposed to shedding	1 per 50 d	Assumed constant here but is really temperature-dependent
A	Additional mortality rate of shedding snails due to infection	1 per 10 d	(3)
λ	Daily infection probability from snail to man, an aggregate parameter that includes cercarial shedding rate divided by cercarial mortality and probability of parasite survival to patency in humans	0.0005	Little data available, calibrated to match expected behavior of the system; compared with estimates (5): ~ 1 infection per 127–1,176 water contacts per person
k	Dispersion parameter of the negative binomial distribution	0.25	Estimated using data from Yousif et al. (6) and from this project
μ_a	Adult worm natural mortality	$1/3 * 365 \text{ d}$	Estimated life span of 3.3 y (range: 2.7–4.5 y) from Shiff et al. (7)
D	Mortality of adult worms due to rate of human mortality	$1/60 * 365 \text{ d}$	Assume an average human life expectancy of 60 y

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Table S2. Observed and predicted (by our model) percentage difference in *S. hematobium* human disease prevalence and egg burden at the experimental site compared with the control site across all follow-up time points

Parameter	Observed				Predicted
	5 mo, %	12 mo, %	18 mo, %	Mean difference \pm SE, %	Mean difference, %
Prevalence	-20	-8.2	-25.6	-17.9 \pm 5.1	-23.6*
Egg/worm burden	-36.3	-50	-63.5	-49.9 \pm 7.9	-56.5 [†]

*Model predicts prevalence of those people with at least two worms (one worm pair), whereas the field data measure the number of people with eggs encountered in 10 mL of urine as a proxy.

[†]Model predicts actual worm burden, whereas field data measure mean eggs per 10 mL of urine as a proxy.

Table S3. Water contact reporting

Village	Study site % (CI)	Rice fields % (CI)	Garden % (CI)
Lampsar 1 (intervention site), <i>n</i> = 152	98% (95–100%)	41% (34–49%)	55% (47–63%)
Lampsar 2 (control site), <i>n</i> = 115	100% (97–100%)	52% (43–61%)	64% (55–73%)

Results of an informal query of all enrolled participants during a site visit in 2013 regarding their reported water contact in the study village's designated water access point (study site), individual rice farming allotments when the paddies were flooded (rice fields), or while collecting water to irrigate vegetable garden plots outside the study village (garden). From 40% to 60% of participants at both the intervention and control villages reported having some water contact outside the study site (in or near rice or garden plots). Shown in the table are the percentages of participants who reported having water contact at the three locations (with the CIs). *n*, number of respondents at each site.