



Cellular Immunity and Resistance to Schistosomiasis in the Philippines (CRISTAL)

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ABSTRACT

- Schistosomiasis remains a major public health problem in the Philippines, with two million Filipinos infected and 12 million of the population at risk of infection [1]. Very high prevalence rates have been recently reported in a number of endemic provinces in the Philippines.
- Schistosoma japonicum* (*Sj*) is the sole schistosome species in the Philippines. The disease is caused by other species in other countries: *S. mansoni*, *S. mekongi*, *S. intercalatum*, and *S. haematobium* [2].
- Acquired by water contact, through the freshwater snail intermediate host (*Oncomelania hupensis quadrasi*). Adult worms establish in the mesenteric veins, where the female worm produces eggs that are subsequently trapped in the liver and induce potent granulomatous inflammatory responses, leading to hepatosplenomegaly and fibrosis.
- The use of Praziquantel has significantly reduced mortality and severe end-organ morbidity, with most countries adopting annual mass drug administration (MDA) [2].
- However, complicating the situation is the fact that *Sj* is a zoonosis, and can infect a wide array of animals such as dogs [3], wild rats, cattle, and in particular, water buffaloes [4].
- Thus, it is evident that the incidence, prevalence, and morbidity of the disease will not be controlled by MDA alone and there is a need for innovative cost-effective strategies, such as vaccines, to control schistosomiasis in the long term.



- Main Objective:** To assess the role of immune cells in resistance or susceptibility to *Schistosomiasis japonicum* reinfection in the Philippines before and after treatment with Praziquantel.
- Schistosomiasis infection status 16 months following treatment was determined by Kato-Katz examination of stool. The intensity of infection (continuous eggs per gram of stool) was also assessed. These outcomes will be associated with various immune parameters.

METHODOLOGY

The study design is a longitudinal, observational study. Three hundred forty six individuals ages 10 to 50 years old and infected with schistosomiasis were enrolled into the study. Another set of 60 Schisto-negative healthy individuals who have never travelled to a schistosomiasis-endemic area were enrolled to serve as normal controls.

- (1) Community preparation, courtesy calls, and barangay assembly for the orientation of the study



- (2) GPS mapping of all households, house tagging, and conduct of household census interview via tablets for paperless entry



- (3) Consent signing activity of target participants for stool screening



- (4) Stool screening using three stool Kato-Katz technique for all consenting villagers 10-50 years old; a barcoded sample tracking database was used to monitor submission compliance



- (5) Schisto-positive consented participants were invited to the satellite laboratory for Study Visit 1 activities: liver ultrasound, physical examination, Praziquantel treatment, blood collection, PBMC isolation, water contact activity interview, urine CCA test, nutritional measurements, and main study consent signing; with majority of the activities recorded on a networked tablet database





- (6) Follow up visit, 4 weeks after Praziquantel treatment for: socio-economic status interview, phlebotomy work, water contact activity interview, urine CCA test, Albendazole treatment; with majority of the activities recorded on a networked tablet database

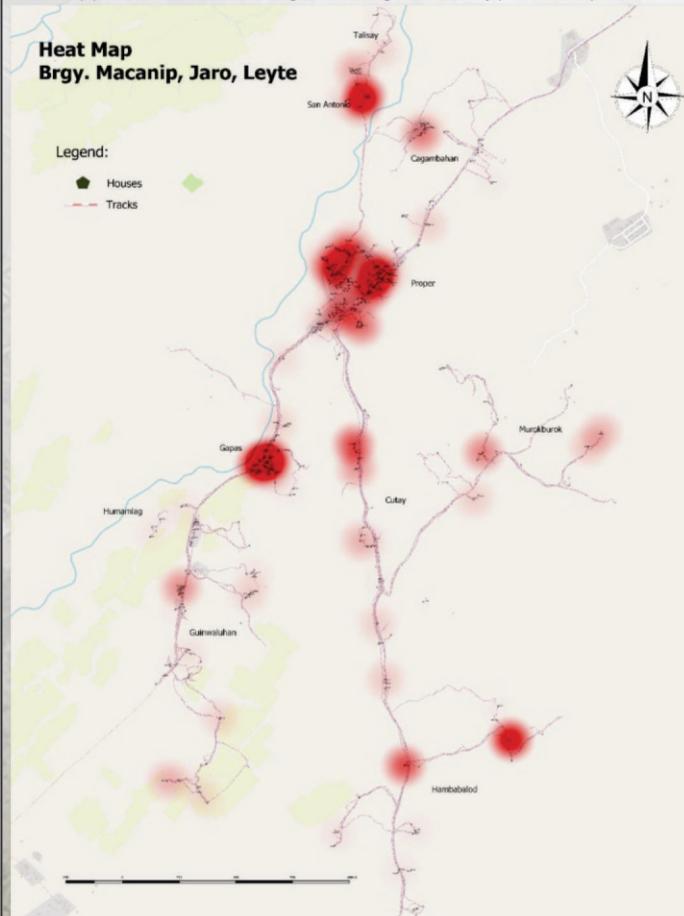


- (7) Close out visit, 16 months after study initiation for: liver ultrasound, physical examination, Praziquantel treatment, phlebotomy work, water contact activity interview, urine CCA test, pregnancy test, nutritional measurements; with majority of the activities recorded on a networked tablet database

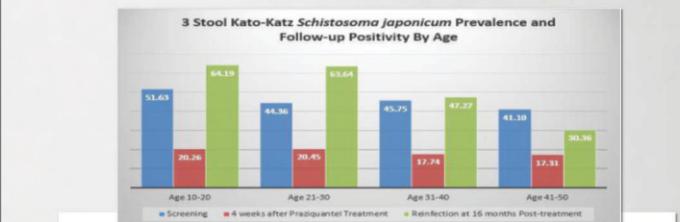


RESULTS

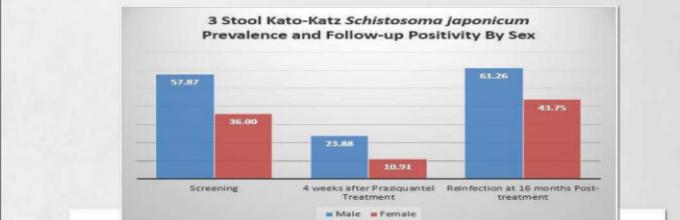
- Heat map produced from stool screening data showing *Schistosoma japonicum* hotspots:



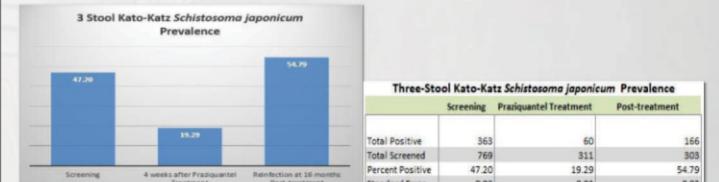
Sitio	Three-Stool Kato-Katz <i>Schistosoma japonicum</i> Prevalence by Sitio			
	Screening	4 weeks after Praziquantel Treatment	Reinfection at 16 months Post-treatment	
Cagabulan	Total Positive	Total Screened	Percent Positive	Standard Error
Cutay	27	59	54.00	0.07
Gatas	50	112	44.64	0.05
Guimbaluan	17	26	65.38	0.09
Hambalod	29	54	53.70	0.07
Humamlag	29	73	39.73	0.06
Murokburuk	16	27	59.26	0.09
Proper Zone 1	61	116	52.59	0.05
Proper Zone 2	68	141	48.23	0.04
Proper Zone 3	21	86	24.42	0.05
San Antonio	7	11	63.64	0.15
Talisay	17	28	60.71	0.09
	Total Positive	Total Tested	Percent Positive	Standard Error
	19	40	47.50	0.10
	15	24	62.50	0.08
	13	22	59.09	0.10
	17	36	47.22	0.06
	24	44	54.55	0.08
	11	26	42.31	0.10
	Total Positive	Total Tested	Percent Positive	Standard Error
	19	42.31	45.45	0.11
	22	54.55	54.55	0.11
	27	55.10	55.10	0.07
	30	58.82	58.82	0.07
	6	15	40.00	0.13
	8	15	53.33	0.13



Age Grp (Years)	Screening				4 weeks after Praziquantel Treatment				Reinfection at 16 months Post-treatment			
	Total Positive	Total Screened	Percent Positive	Standard Error	Total Positive	Total Tested	Percent Positive	Standard Error	Total Positive	Total Tested	Percent Positive	Standard Error
10 to 20	174	337	51.63	0.03	31	153	20.26	0.03	95	148	64.19	0.04
21 to 30	59	133	44.36	0.04	9	44	20.45	0.06	28	44	63.64	0.07
31 to 40	70	153	45.75	0.04	11	62	17.74	0.05	26	55	47.27	0.07
41 to 50	60	146	41.10	0.04	9	52	17.31	0.05	17	56	30.36	0.06



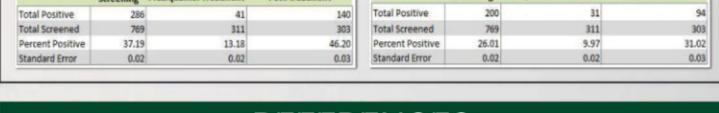
Sex	Screening				4 weeks after Praziquantel Treatment				Reinfection at 16 months Post-treatment			
	Total Positive	Total Screened	Percent Positive	Standard Error	Total Positive	Total Tested	Percent Positive	Standard Error	Total Positive	Total Tested	Percent Positive	Standard Error
Male	228	394	57.87	0.02	48	201	23.88	0.03	117	191	61.26	0.04
Female	135	375	36.00	0.02	12	110	10.91	0.03	49	112	43.75	0.05



Screening	4 weeks after Praziquantel Treatment				Reinfection at 16 months Post-treatment			
	Total Positive	Total Screened	Percent Positive	Standard Error	Total Positive	Total Tested	Percent Positive	Standard Error
Total Positive	363	769	60	0.02	19	311	50	0.03
Total Screened	769	769	100	0.02	19	19	100	0.02
Percent Positive	47.20	19.29	54.79	0.02	19	311	50	0.03
Standard Error	0.02	0.02	0.02	0.03	0.02	0.02	0.02	0.03



Screening	4 weeks after Praziquantel Treatment				Reinfection at 16 months Post-treatment			
	Total Positive	Total Screened	Percent Positive	Standard Error	Total Positive	Total Tested	Percent Positive	Standard Error
Total Positive	286	41	68.54	0.02	140	201	70.00	0.03
Total Screened	769	111	70.00	0.02	140	303	46.20	0.03
Percent Positive	37.19	13.18	46.20	0.03	140	303	46.20	0.03
Standard Error	0.02	0.02	0.02	0.03	0.02	0.02	0.02	0.03



Screening	4 weeks after Praziquantel Treatment				Reinfection at 16 months Post-treatment			
	Total Positive	Total Screened	Percent Positive	Standard Error	Total Positive	Total Tested	Percent Positive	Standard Error
Total Positive	200	31	65.00	0.02	94	141	65.00	0.02
Total Screened	769	311	65.00	0.02	94	303	65.00	0.02
Percent Positive	26.03	9.87	31.02	0.02	94	303	31.02	0.02
Standard Error	0.02	0.02	0.02	0.03	0.02	0.02	0.02	0.03

REFERENCES

- Jiz, Mario, Haiwei Wu, Remigio Olveda, Blanca Jarilla and Jonathan D. Kurtis. Development of Paramyosin as a Vaccine Candidate for Schistosomiasis. *Front. Immunol.* (6)347 July 2015 doi:10.3389/fimmu.2015.00347
- Hannah Wei Wu, Zhi-Qiang Fu, Ke Lu, Sunthorn Pond-tor, Rui Meng, Yang Hong, Kai Chu, Hao Li, Mario Jiz, Jin-Ming Liu, Ming Hou, Sangshing Park, Jiao-jiao Lin, Jonathan Kurtis. Vaccination with recombinant paramyosin in Montanide ISA206 protects against Schistosoma japonicum infection in water buffalo. *Vaccine* 35 (2017) 3409-15.
- Fabre V, Wu H, Pondtor S, Coutinho H, Acosta L, Jiz M, Olveda R, Cheng L, White ES, Jarilla B, McGarvey ST, Friedman JF, Kurtis JD. Tissue inhibitor of matrix-metalloproteinase-1 predicts risk of hepatic fibrosis in human Schistosoma japonicum infection. *J Infect Dis.* 2011 Mar 1;203(5):707-14. Epub 2011 Jan 3.
- Shaw JG, Aggarwal N, Acosta LP, Jiz MA, Wu HW, Leenstra T, Coutinho HM, Olveda RM, Kurtis JD, McGarvey ST, Friedman JF. Reduction in hookworm infection after praziquantel treatment among children and young adults in Leyte, the Philippines. *Am J Trop Med Hyg.* 2010 Aug;83(2):416-21.