Article ID: 2019-0057		
Title: The cost-effectiveness of schistosomiasis screening and treatment among recently resettled refugees to Canada		
Authors: John Webb, Gabriel Fabreau, Eldon Spackman, Vaughan, Stephen, Kerry McBrien		
Peer review comments:		
Reviewer 1: Dr. Thomas Piggott, McMaster University, Hamilton, Ont.		
Reviewer comments	Author response	
1 . The biggest challenge I see with the model as presented is that sufficient data and rationale for assuming no disutilities associated with praziquantel treatment is provided. Adverse effects of treatment constitutes the main non-cost difference between presumptive treatment, and test and treat. Despite their short duration they are common in asymptomatic individuals (according to the limited literature) and given the marginal difference in incremental QALYs between these two arms could constitute an important difference in the models; they should be analysed or a more robust rationale for excluding them should be provided.	I agree that adverse effects of treatment constitute the main non-cost difference between presumptive treatment compared to screening and treatment. For us the difficult question was whether it would be of significant enough magnitude to require modelling. Considering that the duration of side effects would be a few days at most, and that the model has a lifetime horizon, we assumed the mathematical product of a small change in utility preference over a very small portion of the time horizon would result in an insignificant loss of utility for individuals. I've tried to express this concisely by adding the following sentence to the Methods section:	See the following sentence in the Methods section, page 5. "We did not attempt to estimate the disutility of side effects associated with a one-day course of praziquantel, because by virtue of being mild and lasting a few days, they were assumed to be negligible."
2. Gamma distributions are typically reserved for costs, while a lognormal distribution is considered for disutilities; you have used gamma.	The decision to use gamma distributions for disutilities instead of lognormal was somewhat arbitrary. We were aware that both "*Decision Modelling for Health Economic Evaluation*" by Briggs, Claxton and Sculpher and the CADTH Guidelines for the Economic Evaluation of Health Technologies recommend either gamma or lognormal distributions for skewed data such as costs and utilities. We chose to use gamma distributions because we were already comfortable with how to parametrize the distribution in Excel and the	

	aforementioned guidelines suggested either distribution could be used.	
3. Cost of schisto ELISA was parameterized from foreign estimates (with currency conversion). The appropriate provincial lab costs in Canada should ideally be estimated and used in lieu of these estimates.	Thank-you for identifying an issue that was poorly described in this draft of the paper. Though it is somewhat counter-intuitive, we believe the foreign estimates are the most accurate estimates of what the true cost of testing is in Canada. To clarify: provincial laboratories do not perform the test for schistosomiasis. All samples are sent to the National Reference Centre for Parasitology (NRCP) at McGill University. Technically, the NRCP does not charge for the test, but recovers some of its costs from fees charged for other tests. The NRCP was unable to provide an accurate cost estimate as it has not calculated its costs for performing the schistosomiasis test. The director of the NRCP referred us to other national labs that perform the same test, and that charge a fee based on their actual costs, as the best approximation of the cost of testing at the NRCP. I have attempted to explain this by expanding the following section in Appendix 1.	Please see the following paragraph in Appendix 1. "It was necessary to estimate costs of laboratory testing using estimates from labs in countries other than Canada. All testing for schistosomiasis is done at Canada's National Reference Centre for Parasitology (NRCP), however the NRCP could not provide the authors with an estimate of the cost of testing, nor does the NRCP charge clients for schistosomiasis testing. However, in a conversation on February 1, 2018 the laboratory director, Dr. Momar Ndao, suggested the true cost to the lab would be comparable to what it is for other national laboratories. The authors contacted two laboratories. In an email sent May 24, 2018, Jayne Jones of the Liverpool School of Tropical Medicine confirmed the internal cost of the ELISA assay for schistosomiasis at the School`s laboratory was £35.71. In an email sent June 13, 2018, the department of public inquiries for the CDC`s Division of Parasitic Diseases and Malaria confirmed the internal cost of the same assay at its laboratory was $67.00 USD. These amounts were converted to Canadian dollars. These two prices were treated as upper and lower limits, and the cost of the schistosomiasis screening test was modelled in a uniform distribution between them."
4. No rationale for a 20-year time horizon provided for the model.	Thank you for identifying an error that we missed while editing the paper. The sentence that said we used a 20-year time horizon	Please see Methods section, page 5.

	should not have been in the paper, because we did not use that horizon. That sentence was an artifact of an earlier version of the paper that was written when the model was in development, and we must have overlooked it while editing. As stated earlier in the paper, the time horizon was individuals' lifetimes, which varied in different iterations of the model, depending on their clinical course, as explained in the Methods section.	
5. Formatting work needs to be done to improve Figure 1 - arrows and lines.	We would be happy to work with the editors to reformat Figure 1 as required.	
6. Missing appendix title for the CHEERS checklist.	This has been corrected, thanks.	
Reviewer 2: Dr. Murray Dale Krahn, Toronto General Hospital, Medicine, Toronto, Ont.		
Reviewer comments	Author response	
1. Why was not treatment in Africa prior to arrival in Canada not included as one of the strategies...?	This is a valid question, and we have another manuscript in progress that makes the case for pre-departure treatment in Africa. However, for this paper we limited our scope to the screening and/or treatment options that are currently feasible without a policy change at the level of Immigration, Refugees and Citizenship Canada. To deal with this question more directly, I have added the following section to the Introduction section:	Please see the following sentence in the Introduction, on page 2. "Our model only considered presumptive treatment as an option for refugees who have already arrived in Canada, because this is an option that Canadian health care providers can provide if they choose to do so. Presumptive treatment prior to departure is also an option worth considering, but to implement it would require changes in government policy."
2. Why assume that patients would present to hospital in a single episode...this seems simplistic. I would bet that many patients would get a lot of outpatient care and tests over a long period of time- much of this, I would expect, will happen in an outpatient setting	I agree that our assumption that patients would initially present with symptoms that would require hospitalization may be an oversimplification, but there is some evidence that supports it. The case reports we found of schistosomiasis among immigrants to non-endemic countries describe individuals who were hospitalized, and this influenced our	See Limitations section, page 11

	assumption. It would be fair to say the absence of case reports of patients who received outpatient care may simply reflect a form of publication bias. Because it's difficult to be certain what assumption about patterns of health care use is correct, we have been as transparent as possible about the assumptions that were made. I've attempted to address this in the Limitations section of the paper. The cost of outpatient care that follows a hospitalization has been taken into account in our model.	
3. There is a very complex representation of all of the potential complications of disease, but - I would bet that many patients have more than one complication...how is this handled?	We attempted to model multiple complications by allowing for combinations of complications that we considered most likely. It's possible for individuals with urinary disease to have up to 2 complications: 1) obstructive disease or genital infection; and 2) bladder carcinoma. Individuals with hepatosplenic schistosomiasis can have up to 3 systems affected: 1) portal hypertension with or without ascites; 2) intestinal disease or no intestinal disease; and 3) cardiac, pulmonary, renal, or CNS involvement. To reduce the word count, we had relied on Figure 1 to convey that information. We would be happy to add some explanatory text if the editors agree.	
4. What is the acceptability to patients of empiric treatment without a specific diagnosis....is there evidence to support a 90% adherence rate.	We assumed that because many refugees come from countries where mass prophylaxis programs against schistosomiasis are common, treatment acceptance would be similar to what it is currently estimated to be in the clinic for treatment after a positive test. The data from the MOSAIC clinic shows that 229 of 261 patients with a positive diagnostic test, or 88%, had received a prescription. The 90% used earlier had been an estimate based on an earlier dataset. We ran the model again using 88%, and the results did not not change. The	Please see the following sentence in the Methods section on page 4. "We assumed 88% of patients with a positive test would take praziquantel, based on clinic data on the proportion of patients with a positive diagnosis who also had a prescription for praziquantel."

	results also didn't change in a one-way sensitivity analysis in which we assumed only 50% of patients with a positive test would take praziquantel. This would allow for the possibility of many patients not filling prescriptions.	
4. Importantly- using Canadian life expectancy estimates for a refugee population is almost certainly wrong. Are there no data that could be used to adjust LE estimates for the burden of comorbid disease that refugees bring with them?	Ironically, the studies we found on life expectancy of refugees suggested it is longer, but they acknowledge that may be due to selection bias. Their data sources could have excluded marginalized refugees. Our choice was to use average Canadian life expectancies, and vary the annual probability of dying from complications in our sensitivity analysis. This was equivalent to varying the life expectancy for sick individuals. We did not vary the life expectancy for healthy individuals, but because we both increased and decreased it for sick individuals, our model would have capture both the scenarios where the difference between life expectancies for both groups is larger or smaller. The model results did not change.	
6. Not super essential to me, but pretty common to see a CEAC curve to summarize results...	We agree. The CEAC curve is currently in Appendix 4. We would be happy to move it to the main manuscript at the editors' request.	Please see Appendix 4
7. p.11 there's an "x,y,z" that was left in from a draft version of the ms	Our apologies for missing that in editing. I've removed it.	Please see page 11
8. The ongoing care costs of these complications seem implausibly low to me- having done detailed costing of CHF, HCV etc, once there is a diagnosis established of a major organ complication (cor pulmonale, liver disease, bladder cancer) the ongoing costs are in the thousands. Sometimes, simplistic microcosting, as has been done here, is necessary because there are no data. But- there are published data for cancer of	We agree that this is a limitation of the paper. The hospital care costs underestimate the true cost because they are taken from the Canadian Institute for Health Information's patient cost estimator, which does not include physician fees. We used this data source because we could not identify cost-of-care studies published for all the different possible complications of schistosomiasis, or their analogues. We did not feel comfortable including care costs derived using different methods for different complications; many of	Please see Limitations section page 11

different types, liver disease etc. The numbers here are way off...I'd encourage a more careful look at the CDN literature for relevant cost estimates.	which had no Canadian-specific detailed cost estimates. Further, although Canadian cost estimates have been reported for diseases such as CHF, liver disease and bladder cancer, these represent the common disease manifestations in the Canadian population. Complications of schistosomiasis have unique disease trajectories (for instance, the liver disease is more closely approximated to portal hypertension than cirrhosis), and we therefore felt more comfortable with a conservative estimate. I have added a clarification about this difficulty in the Limitations section of the paper. We agree with the reviewer's comments: underestimating the cost of care does not invalidate the results of the study, because it biases them toward the null hypothesis. However, it's necessary to acknowledge the hospital costs are lower than they would be in reality.	
9. Putting a higher price tag on complications will not change the qualitative result- empiric treatment will be even more cost effective. But....it makes the analysis look weak if frankly implausible numbers are included.	As discussed above, we've attempted to address this by acknowledging it as a limitation of the study.	Please see Limitations section page 11
10. Care pathways in table 1 seem just wrong to me. Propranolol for PHT? I haven't seen that for years. Just lasix for cor pulmonale. I think this section really needs a look from some clinicians....seems implausibly simple	This is a valid criticism, and I hope the appropriate response is to be transparent about what assumptions we made. It may be that our care pathways do not accurately reflect current practices, but we hoped they would because they were taken from clinical guidelines published by the American Association for the Study of Liver Diseases, the Canadian Cardivascular Society, Kidney Disease: Improving Global Outcomes, and the Canadian Urological Association; and reviewed by a clinician who treats refugees. When recommendations varied by severity of	Please see Limitations section page 11

	disease, we used recommendations for disease of mild severity, to avoid overestimating the cost of treatment. I have added a clarification about this to the limitations section of the paper. If I may respond to your concern about propranolol for pulmonary hypertension: the table describes Diltiazem being given for PHT, and propranolol being given after variceal hemorrhage.	
11. I am sorry to say also that the disutilities seem way off. For example, if you have ascites, this means you have decompensated liver disease. Your function is dramatically affected.... few people with ascites can work...they are often in the hospital for treatment and often have other complications like variceal hemorrhages, infections, encephalopathy etc. There are good published utilities for this stuff.	I'd like to respond in two parts: first regarding the research from which we derived our utility preferences; and second regarding your specific concerns about the utility preference associated with ascites. Because our model had many different disease complications, we chose to use two catalogues of utility preferences for a range of disease states, calculated by the same authors, which ensured the same methods were used for each disease state. This restricted us from using studies specific to certain diseases, which may in some cases have been more valid for a specific disease but would create issues when multiple diseases are considered in the same model. Regarding the disutility associated with ascites: although our first inclination was to use a disutility similar to what would be expected in decompensated liver cirrhosis, the best evidence we could find is that schistosomiasis causes portal hypertension without cirrhosis, and the associated ascites has much less effect on function. This point is made in the paper by the Brazilian author Reboucas, "*Clinical aspects of hepatosplenic schistosomiasis: a contrast with cirrhosis*", which is listed in the references. Again, you raise a valid criticism about whether the model underestimates disutility.	Please see Limitations section page 11

	This was a choice made by the authors in an attempt to be conservative towards the cost-effective option. Our response is to acknowledge that this may be the case, but we agree with you that despite this limitation, our conclusions would not change if the disutilities were greater.	
12. The validation section does not describe model validation...it is simply a validation of a single parameter in the model.	We chose to only describe the external validation of the model. The steps are described in more detail in Appendix 2. We didn't describe the internal validation steps, which included many different logical checks such as ensuring all the utilities for sick individuals were lower than for healthy individuals, that life spans for sick individuals were the same or less than healthy individuals, that costs for individuals who were tested or treated were higher than for those who were not, etc. We can include these if the editors feel they are important to add.	
13. Finally, this is a pretty Calgary-centric paper. There is almost no discussion of how this applies outside of Calgary, apart from an analysis of prevalence. What's different in Montreal or Vancouver or Halifax or Toronto or Boston or Barcelona....to whom is this analysis applicable....	We believe our results are generalizable to other cities, but the paper may not have effectively communicated the reasons why. There are five parameters in the model that were estimated in the Calgary refugee population: the prevalence of infection, mean age, male-to-female ratio and approximate ratio of hepatosplenic to urinary disease (which depends on countries of origin), and the treatment acceptance rate. We assumed mean age and male-female ratio would not be significantly different in other communities, but that prevalence and ratio of hepatosplenic to urinary disease could be different. This may not have been explained clearly in the paper. I've added the following section to the Methods. We claimed our results would be generalizable to other Canadian communities, where prevalence and disease type might be different, but presumably health costs are similar.	Please see the following sentence in the Methods section, page 3. "Because disease prevalence could be different in other communities, to increase the generalizability of our results we used a prevalence range of 0-30% in a subsequent exploratory analysis. We also varied both the ratio of hepatosplenic to urinary disease (which reflects variation among origin countries), and treatment acceptance, as described in a sensitivity analysis below."