## Introduction

Schistosomiasis, or infection with schistosomes, is a relatively unknown disease in Canada. It is a chronic parasitic infection that only affects people who have visited or lived in endemic regions such as the Middle East, Asia, Caribbean, and Africa, where it is a common cause of chronic disease.[1] Because it persists in conditions of poverty, the World Health Organization considers it a neglected tropical disease.[1] It is contracted through exposure to freshwater contaminated with schistosomes, a naturally occurring parasite. They penetrate the skin, migrate into the circulatory system, and secrete eggs into the bloodstream. This continues throughout the parasite's lifetime. Long-term complications arise from schistosomes depositing their eggs, which are highly immunogenic, into their host's systemic and pulmonary circulation.[2]

Refugees are disproportionately affected due to poor access to safe water and health care prior to resettlement. [3, 4] They may be asymptomatic when they arrive in their new country, but 12%- 73% have latent infection.[5-11] Inflammation and fibrosis caused by accumulation of eggs in various organ systems put patients at risk for gastrointestinal, pulmonary, central nervous system, genitourinary and other long-term complications. [2, 12-17]

In 2011 the Canadian Collaboration for Immigrant and Refugee Health (CCIRH) recommended screening and treatment for refugees from Africa for schistosomiasis.[18] The CCIRH acknowledged there was limited evidence this strategy is effective , and there has been incomplete adoption of its recommendations in Canada. In Australia, the Australasian Society

for Infectious Diseases (ASID) recommends screening and treatment of refugees from not only Africa, but also parts of Asia and the Middle East.[19] In the United States, the Centers for Disease Control (CDC) has a policy to presumptively treat for schistosomiasis before refugees leave Africa.[20] While practices vary, neither the cost-effectiveness of presumptive treatment nor that of screening and treatment for schistosomiasis has ever been studied. Yet the number of displaced persons worldwide is at its highest level since the United Nations High Council of Refugees was created.[21] To inform practice, we modelled the relative costs and benefits of watchful waiting, screening and treatment, and presumptive treatment.



## Methods

### Study cohort

We gathered data from the Mosaic Refugee Health Clinic (MRHC), which provides care for the majority refugees and asylum claimants in Calgary, Alberta, Canada. The clinic implemented the CCIRH guideline in 2011, extending its screening protocol to all refugees. We modelled a hypothetical cohort of 1000 refugees whose sex, region of origin, mean age and prevalence of infection was the same as refugees seen at the MRHC between 2011 and 2015. Disease prevalence and patient demographics were obtained from clinical records of patients seen at the clinic during this time period. Data collection was approved by the Conjoint Health Research Ethics Board of the University of Calgary. Because disease prevalence could be different in other communities, we also used a prevalence range of 0-30% in a subsequent exploratory analysis.

## Treatments considered

We assumed patients who were treated for latent infection would be given a one-day course of praziquantel. Praziquantel is an antiparasitic medication that is taken at a total dosage of 40mg/kg in one to three divided doses over the course of a single day. Reported cure rates using this protocol vary between 81% and 95%.[22] It is well tolerated though some patients experience minor and transient side effects including: gastrointestinal symptoms, nausea, fatigue and dizziness. [23] We assumed these would not have a significant impact on quality of life. Because treatment lasts one day, we assumed side effects would not prevent individuals from finishing treatment. We further assumed there was no risk of treatment-resistant strains of schistosomiasis emerging, because the organism does not reproduce outside of endemic areas.

## Management strategies

Our model compared three management strategies.

### *Watchful waiting (status quo)*

Under watchful waiting, we assumed patients would present to hospital if they developed symptoms, and would be treated for complications of schistosomiasis, including: malabsorption, ascites, esophageal varices, glomerulonephritis, pulmonary hypertension, cancer of the bladder, hydronephrosis, pyelonephritis, genital infection, infertility, and central nervous system (CNS) involvement.[2, 12-17] We assumed for certain complications that patients would then be followed by a family physician and a specialist to manage complications that persist after discharge (see appendix 1).

### *Screening and treatment*

Under screening and treatment, we assumed all newly arrived refugees would be given a serological test (ELISA) for schistosomiasis offered by the National Reference Centre for Parasitology (NRCP), as is typical at most refugee clinics in Canada. Patients who tested positive would be offered praziquantel. Treatment adherence was assumed to be greater than 90%.

### *Presumptive treatment*

Under this strategy, we assumed newly arrived refugees would be offered praziquantel at their initial clinic visit.

### *Decision model*

Using Excel 2016 software we developed a decision-tree model that assessed the cost-effectiveness of the three strategies for screening and/or treating refugees for schistosomiasis. [24] Our model assigned cohort members to the health states shown in Figure 1, according to the probabilities of progression summarized in Table 1, and either the mean Canadian life expectancy, or a disease-specific life expectancy who those who died from complications of schistosomiasis.

## *Model parameters*

We obtained model parameters (Tables 1 and 2), including disease progression probabilities, survival rates, utility coefficients, test sensitivity and specificity, and treatment efficacy from the literature. Cohort characteristics, including mean age, prevalence of schistosomiasis, sex and region of origin were obtained from clinical records of MRHC patients. To estimate mean life expectancy, we used the Statistics Canada 2015 life table for Canada.[25]

To estimate life expectancies associated with schistosomiasis complications, we used Stata 15 software to fit hazard functions to survival curves taken from disease-specific survival studies (see Appendix 1), then we used a previously published life table method to estimate mean life expectancy for people with specific complications.[26] Costs of hospital-based care were estimated using the Canadian Institute for Health Information (CIHI) Patient Cost Estimator [27]. We estimated community care costs by using the Alberta Health Care Insurance Plan schedules of medical and drug benefits [28, 29] to estimate the cost of managing specific complications according to published guidelines [30-35]. Refugees and refugee claimants purchase praziquantel at a price set by the Interim Federal Health Program (IFHP), which is operated by Medavie Blue Cross on behalf of Canada's Ministry of Immigration, Refugees and Citizenship. [36] The cost of praziquantel ($47.93 per patient) under the IFHP was obtained from selected pharmacies that participate in the IFHP (see footnotes b & c in Table 1). We estimated the cost of schistosomiasis testing at the National Reference Centre for Parasitology (NRCP) by using estimates from selected laboratories that have done full internal costing. Although the NRCP charges $15 for schistosomiasis testing, this does not represent the full cost to the lab. (Refer to Appendix 1 for detailed descriptions of all these parameters.)

### *Economic assumptions*

We conducted our analysis from the perspective of the Canadian publicly-funded health care payer. We included: Alberta Health, which funds labour, materials, clinic overhead, testing and treatment for residents of Alberta; Health Canada, which supports laboratory testing for schistosomiasis; and Citizenship and Immigration Canada, which pays for refugee claimant's health care and refugees' prescriptions for praziquantel, under the IFHP.

### *Outcomes*

We calculated quality-adjusted life years (QALYs) and costs using both a deterministic model with fixed costs and probabilities, and a probabilistic Monte Carlo simulation with variable costs and probabilities. We also calculated Net Monetary Benefit (NMB) using the formula NMB = QALYs*($50,000/QALY) – Cost. (This combines health and cost outcomes into a single metric, by assuming health benefits are valued at $50,000 per QALY.) We used Stata 15 to conduct linear regression of NMB against prevalence and plot linear functions of NMB versus prevalence.[61] Whichever option had the greatest NMB at a given disease prevalence was considered cost-effective at that prevalence. For any two options that were compared, incremental cost-effectiveness ratios (ICERs) were calculated using the formula ICER= (Cost1 – Cost 2) / (QALYs1 – QALYs2); however, if one option was both more effective and less costly than the other, that option was considered to 'dominate' the other option, and no ICER was calculated. We used a 20-year horizon and future costs and benefits were discounted at 1.5% annually, in keeping with the Canadian Agency for Drugs and Technologies in Health (CADTH) guidelines.[54]

### *Sensitivity Analysis*

We performed both 1-way deterministic sensitivity analyses and probabilistic sensitivity analyses, to explore the effects of variation in the model's input parameters. We varied individual probabilities of disease progression; cure; death from schistosomiasis; and hepatosplenic as opposed to urinary disease; as well as the time to onset of complications and the cost of treatment.

# Results

### *Model validation*

Using the model, we predicted the number of patients in Calgary with schistosomiasis in 2017, then compared the prediction to the number of people diagnosed with schistosomiasis in Calgary in 2017, according to the records of Alberta Health Services (AHS). The totals were similar. (Please see Appendix 2 for a detailed summary.)

### *Base case*

In our baseline analysis (Table 3), the probabilistic analysis showed screening and treatment was less costly and more effective than watchful waiting, with a cost savings of $316 and a QALY gain of 0.14 per person. However, presumptive treatment was in turn less costly and more effective than screening, with an additional cost savings of $73 and QALY gain of 0.01 per person. Therefore, presumptive treatment dominated both the screen and treat and watchful waiting options.

Compared to watchful waiting, for a simulated cohort followed for 20 years, screening and treatment reduced the number of deaths from 11 to 2 per 1000 and the number of people living with complications from 88 to 18 per 1000. Relative to screening and treatment, presumptive treatment additionally prevented 1 death and 7 cases of complications per 1000 patients.

### *Sensitivity analyses*

Varying individual input parameters had almost no effect on the results. The results of one-way sensitivity analyses are summarized in Appendix 3. Our probabilistic sensitivity analyses showed, at the baseline prevalence, the chance that presumptive treatment would be cost-effective, relative to watchful waiting and screening, was 100% at any willingness-to-pay (WTP) threshold (see Appendix 4).

### *Scenario analysis*

To allow for the possibility the model overestimated morbidity and mortality, we considered a scenario in which the probabilities of both disease progression and death from schistosomiasis complications decreased to 50% of baseline values, and the cure rate was reduced to 50%. In this scenario, presumptive treatment continued to dominate both screening and treatment and watchful waiting.

### *Exploratory analysis*

Because the prevalence of schistosomiasis may vary between practice settings, we conducted a threshold analysis to determine the prevalence above which both screening and treatment and presumptive treatment, became cost-effective at a willingness-to-pay threshold of $50,000/QALY (see Appendix 5). Figure 2 shows that when prevalence exceeds 0.13%, presumptive treatment becomes cost-effective. Screening and treatment is cost-effective, relative to watchful waiting but not presumptive treatment, when prevalence is more than 0.23%. Presumptive treatment is less costly than screening and treatment at any prevalence. Figure 3 also shows presumptive treatment dominates the other options when prevalence exceeds 2.4%, because it is the least costly. Figure 2 shows that all the differences in NMB

widen with increasing prevalence. Therefore, at the prevalence of 23% found in this study's target population, screening and treatment dominates watchful waiting, and presumptive treatment dominates both watchful waiting and screening.

## Interpretation

Our analysis shows presumptive treatment for schistosomiasis is cost-effective, relative to watchful waiting or screening and treatment, when disease prevalence is greater than 0.13%. Furthermore, once the prevalence is 2.4% or greater, presumptive treatment becomes cost-saving. This threshold is well below the 23% prevalence observed in refugees coming to Calgary between 2011 and 2015 upon whom our model was based. It may be reasonable to assume presumptive treatment would be cost-saving at any clinic that specializes in refugees.

These results are consistent with previous studies, notably that of Muennig *et al* who found domestic presumptive treatment of immigrants to the United States with albendazole, which treats parasites other than schistosomes, would be cost-effective.[62] Following adoption of the CDC's recommendation for presumptive overseas treatment of schistosomiasis, a follow-up study observed a decrease in schistosomiasis among refugees coming to California.[63]

There is a straightforward explanation for the dominance of presumptive treatment over screening and treatment and watchful waiting. While chronic complications of schistosomiasis only happen to a small number of people, they still reduce quality of life and cause premature death, which are costly to health care system. Screening and treatment or

presumptive treatment are inexpensive interventions, costing approximately $50 - $80 per person. In a refugee population where schistosomiasis is common, screening and/or treating every individual costs less than it would to treat the few people who would go on to develop complications if watchful waiting was the norm. Presumptive treatment is always less costly than screening and treatment, because a prescription for praziquantel costs the health care system a few dollars less than laboratory testing. It is always more effective, because without the need for testing, there is no opportunity for false negatives to lead to cases being missed. If refugee clinics such as the MRHC were to implement presumptive treatment over screening and treatment, it would result in an immediate savings of $15 per test for the clinic. The cost of increased prescriptions for praziquantel would then be borne by the IFHC program of the Ministry of Immigration, Refugees and Citizenship, and ultimately the federal government. These increased costs would ultimately be more than offset by savings from prevention of disease. Those savings would nonetheless take decades to realize, since the mean time to onset of chronic schistosomiasis is approximately 20 years.

### *Limitations*

Our model did not include certain costs such as lost productivity, or a loss of utility from short term hospitalization. Including these parameters would have increased the cost-effectiveness of screening and presumptive treatment, which would not have changed the results of the study. Similarly, there is potential for the model to have overestimated the burden of disease associated with schistosomiasis: our external validation showed the model predicted more cases for 2017 than were actually recorded in Calgary the same year. Overestimating the potential burden of disease would have the effect of overstating the

benefits of prevention. However, our sensitivity analyses showed that changing multiple parameters to greatly decrease expected morbidity and mortality would not change the study`s results. The analysis is subject to the accuracy of all model parameters and assumptions made about disease progression; nonetheless, our robust sensitivity analysis tested large variation in numerous parameters and found the model's conclusions did not change.

## Conclusion

Presumptive treatment for schistosomiasis among recently resettled refugees and asylum claimants to Canada is less costly and more effective than watchful waiting or screening and treatment, in groups where disease prevalence is greater than 2.4%. Our results support a revision of the current Canadian guidelines and may inform specialized refugee centres and physicians who treat refugees and asylum claimants in other Canadian cities. In situations where there are barriers or resistance to implementing presumptive treatment with praziquantel, screening and treatment is also less costly and more effective than watchful waiting.

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Figure 1) Simplified decision tree

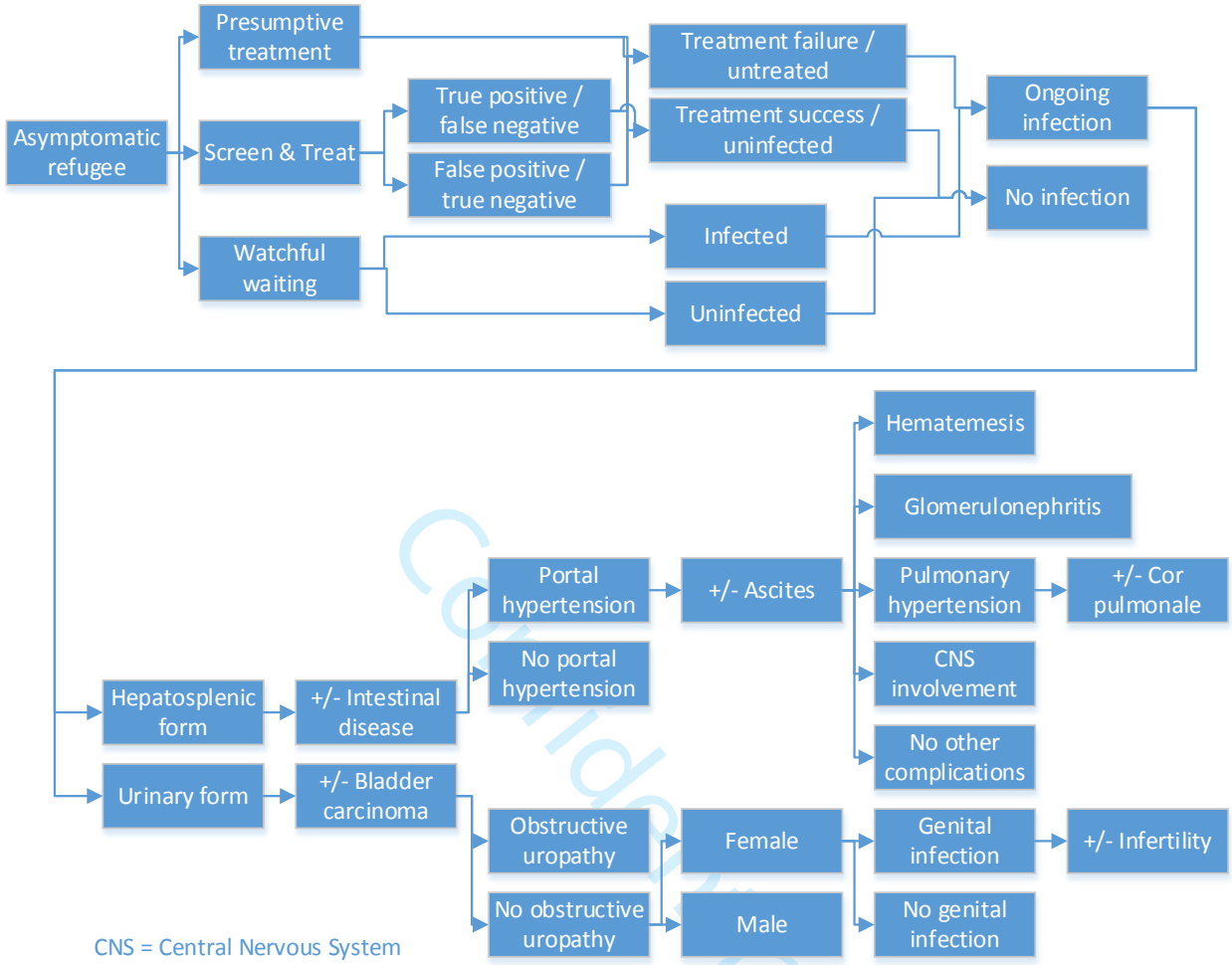

Figure 2a) NMB vs. Prevalence

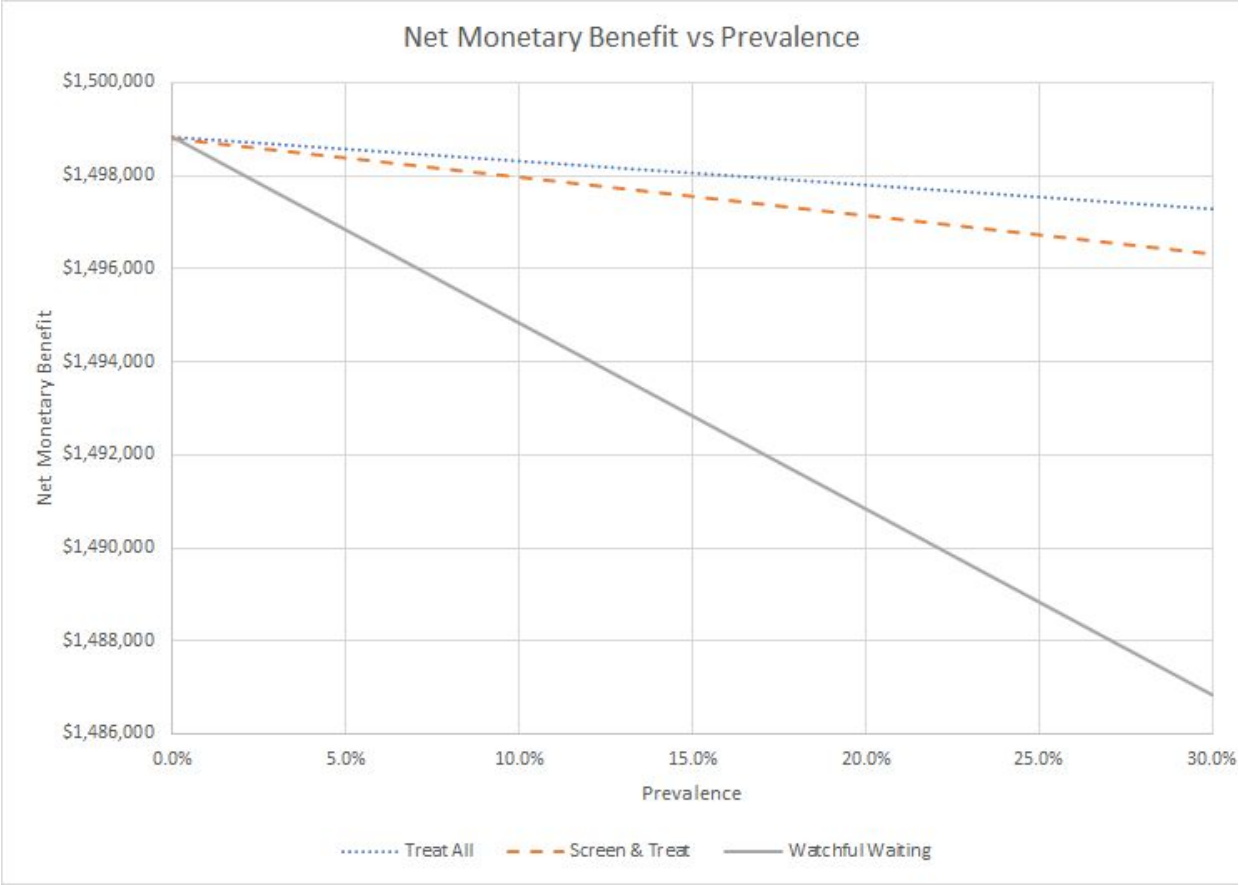

Figure 2b) Detail of figure 2a, scale expanded to show where regression lines intersect

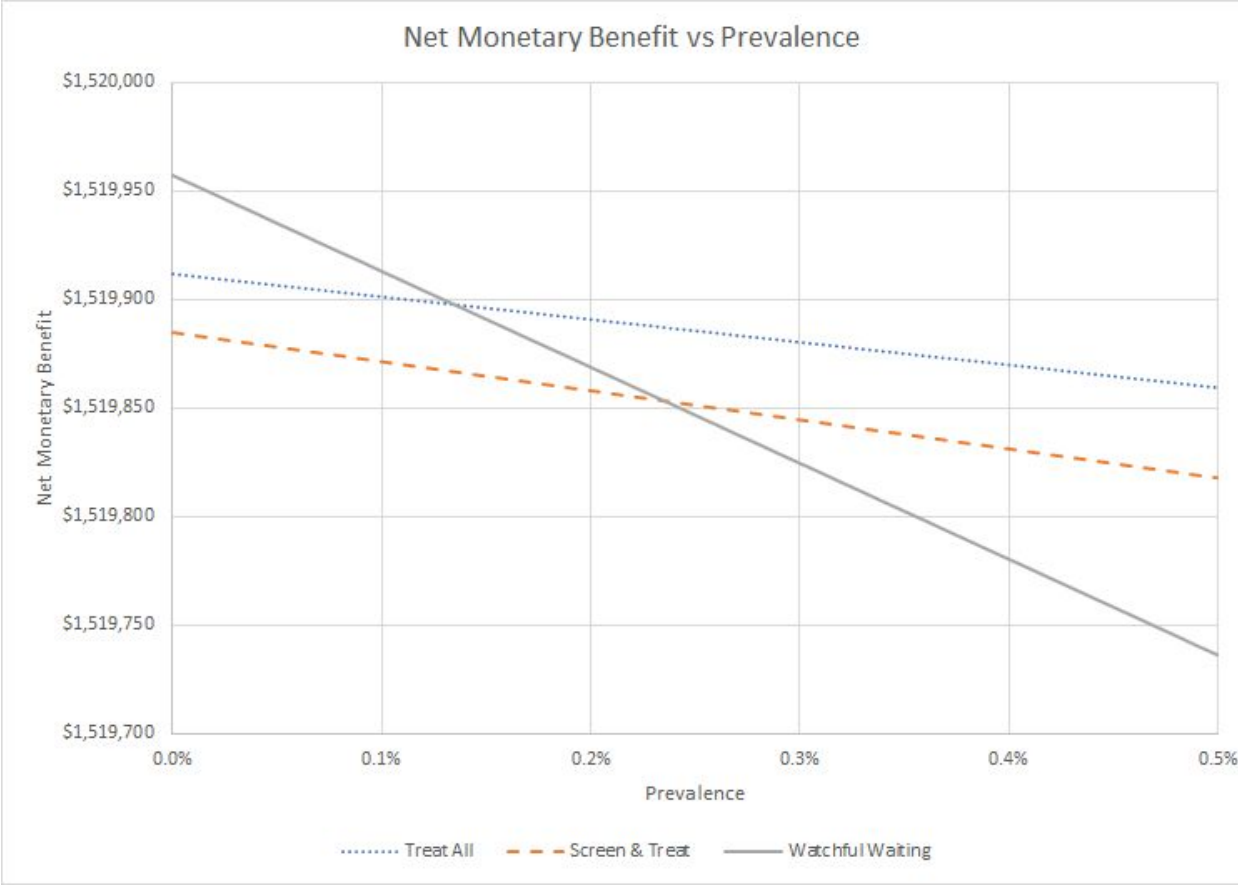

Figure 3) Cost person vs Prevalence

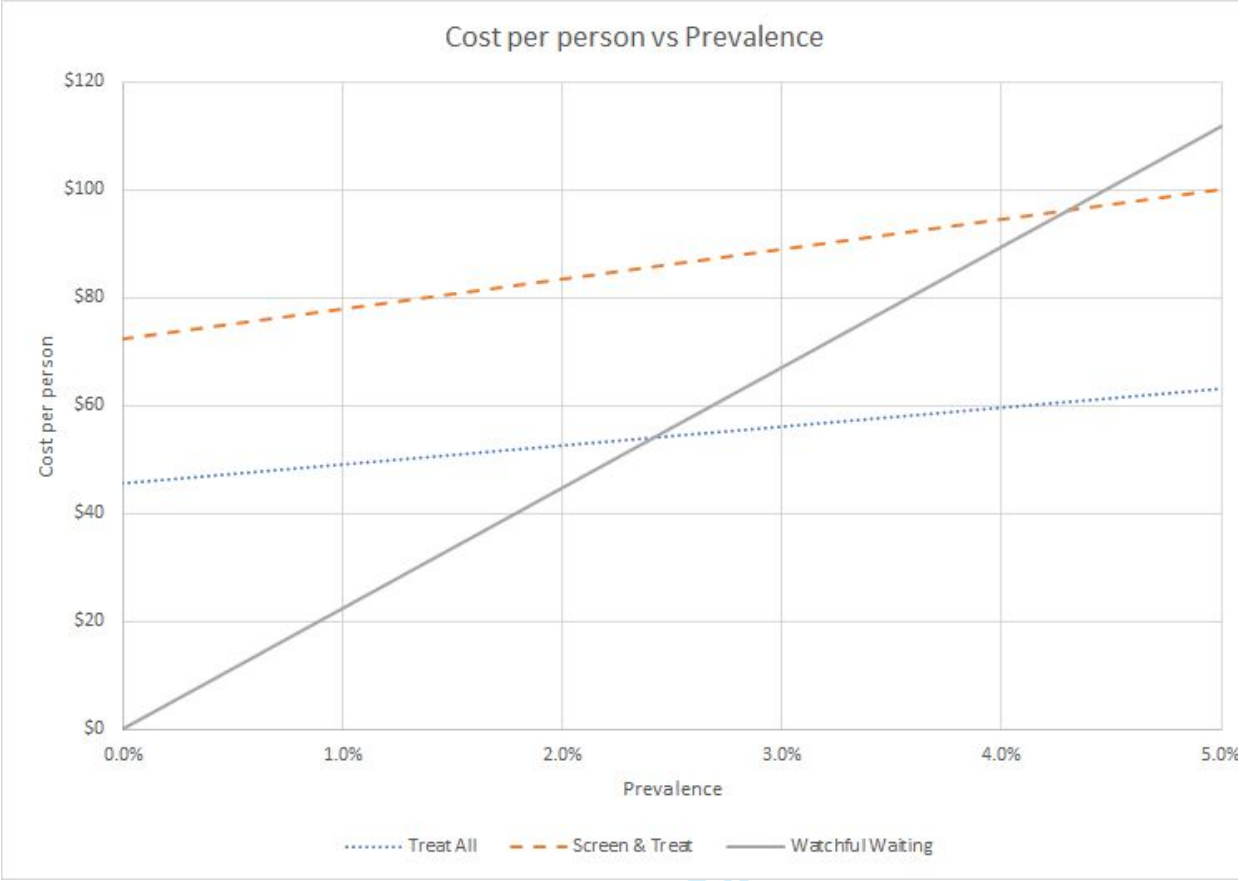

Table 1) Model parameters

| Parameter | Value | Range | Reference |
|---|---|---|---|
| Mean age of patients (yrs) | 35.9 | - | Clinic data |
| Age of symptom onset (yrs) | 55 | 36 - 84 | [37] |
| probability of patient being female | 0.487 | - | Clinic data |
| probability of patient being infected | 0.232 | 0.181 - 0.293 | Clinic data |
| probability of test being (+) given presence of infection | 0.99 | - | [38] |
| probability of test being (-) given absence of infection | 0.90 | - | [38] |
| probability of patient consenting to screening test | 0.98 | - | footnote (a) |
| probability of patient accepting treatment given (+) test result | 0.98 | - | footnote (a) |
| probability of patient being cured by treatment | 0.88 | 0.799 - .929 | [22, 37] |
| probability of hepatosplenic (vs. urinary) involvement, given infection | 0.45 | - | Clinic data |
| probability of urinary obstruction, given infection | 0.287 | 0 - 0.431 | [39] |
| probability of hydronephrosis, given infection | 0.228 | 0 – 0.342 | [39] |
| probability of pyelonephritis, given obstruction | 0.197 | 0 - 0.295 | [39] |
| probability of bacteremia, given pyelonephritis | 0.143 | 0 – 0.341 | [40] |
| probability of genital disease, given infection in female | 0.333 | 0 – 0.500 | [41] |
| probability of carcinoma, given infection | 0.027 | 0 - 0.041 | [39] |
| probability of intestinal disease, given infection | 0.133 | 0 - 0.200 | [42] |
| probability of portal fibrosis, given infection | 0.139 | 0 - 0.209 | [43] |
| probability of ascites, given fibrosis | 0.070 | 0.010 - 0.100 | [44] |
| probability of hematemesis, given fibrosis | 0.027 | 0 - 0.040 | [45] |
| probability of death, given hematemesis | 0.153 | 0 - 0.230 | [46] |
| probability of pulmonary hypertension, given fibrosis | 0.186 | 0 - 0.230 | [42] |
| probability of cor pulmonale, given fibrosis | 0.050 | 0 - 0.075 | [42] |
| probability of glomerulonephritis, given fibrosis | 0.067 | 0 - 0.100 | [42] |
| probability of CNS involvement, given infection | 0.001 | 0 - 0.002 | [43] |
| Survival if no schistosomiasis complications (yrs) | 28.9 | - | [47] |
| Mean survival for glomerulonephritis (yrs) | 17.3 | - | [48] |
| Mean survival for pulmonary hypertension (yrs) | 9.4 | - | [49] |
| Mean survival for bladder cancer (yrs) | 5.3 | - | [50] |
| Mean survival for cor pulmonale (yrs) | 7.0 | - | [51] |
| Mean survival for portal hypertension (yrs) | 27.8 | - | [52] |
| Years of treatment for infertility | 4.1 | - | [53] |
| Utility discount rate (%) | 1.5 | - | [54, 55] |
| Cost discount rate (%) | 1.5 | - | [37, 54] |
| Mean dose of praziquantel (mg) | 1000 | - | footnote (b) |
| Cost of praziquantel ($) | 47.93 | 44.66 – 51.19 | footnote (b) |
| Cost of serology ($) | 74.09 | 61.21 - 86.97 | footnote (c) |

(a) Based on patient data from the MRHC.

(b) Personal communication with David Brewerton, pharmacist at Luke`s Drug Mart in Calgary, AB, and Joel Varsava at Pharmacity in Ottawa, ON. See Appendix 1.

(c) Personal communication with Liverpool School of Tropical Medicine, and CDC Division of Parasitic Diseases and Malaria. See Appendix 1.

Table 2) Disease-related costs and utilities used in the model

| | Hospital Care Cost | Community Care Annual Cost | Utility Decrement | Decrement Range | References |
|---|---|---|---|---|---|
| Ascites | $10,636 | $357 | 0.018 | 0.015 – 0.022 | [27, 30, 33, 56] |
| CNS involvement | $13,289 | $0 | 0 | - | [27, 57] |
| Cor pulmonale | $11,087 | $560 | 0.055 | 0.052 - 0.058 | [27, 31, 51, 56] |
| Glomerulonephritis | $5,441 | $163 | 0.054 | 0.051 – 0.058 | [27, 32, 56] |
| Variceal hemorrhage | $5,714 | $440 | 0 | - | [27, 33] |
| Intestinal malabsorption | $4,441 | $0 | 0 | - | [27] |
| Pulmonary hypertension | $12,706 | $235 | 0.043 | 0.042 – 0.043 | [27, 34, 58] |
| Bladder carcinoma | $6,122 | $362 | 0.017 | 0.017 – 0.018 | [27, 35, 58] |
| Genital schistosomiasis | $4,198 | $0 | 0 | - | [27] |
| Infertility | $0 | $674 | 0.070 | 0.067 – 0.073 | [53, 58-60] |
| Pyelonephritis | $4,576 | $0 | 0 | - | [27] |
| Bacteremia | $18,122 | $0 | 0 | - | [27] |
| Hydronephrosis | $5,441 | $0 | 0 | - | [27] |
| Two comorbities | - | - | 0.091 | 0.090 – 0.092 | [58] |
| Three comorbities | - | - | 0.084 | 0.082 – 0.086 | [58] |
| Baseline health state | - | - | 0.120 | - | [56] |

Table 3) Results of base case

| **Strategy** | **Cost ($)** | **QALYs** | **ΔCost ($)** | **ΔQALYs** | **Sequential ICER ($/QALY)** |
|---|---|---|---|---|---|
| Watchful Waiting | $519 | 29.81 | - | - | - |
| Screening & Treatment | $203 | 29.94 | -$316 | 0.14 | Dominates |
| Presumptive Treatment | $130 | 29.96 | -$73 | 0.01 | Dominates |

# Appendix 1

## Estimation of parameters for the model

### *Cohort demographics*

Patients' mean age, sex and area of origin were obtained from clinical records collected at the Mosaic Refugee Health Clinic (MRHC). The age of symptom onset was estimated using a normal distribution that had the same range and standard error described in a longitudinal study of schistosomiasis among expatriates in a non-endemic country.[1]

### *Model probabilities*

Based on the experience of physicians at the MRHC, patients' acceptance of screening and/or treatment was estimated to be 92% and 95%, respectively. The probability of a patient being infected with schistosomiasis was obtained from data collected from 920 patients at the clinic between 2011 and 2016.[2] The probability of being infected with either the hepatosplenic form or the urinary form of the disease was approximated by the following method: using information about geographic distribution of types of schistosomiasis, it was assumed that among patients who develop disease, those from Africa would have a baseline 50% probability of developing hepatosplenic disease, and a 50% probability of developing urinary disease. It was assumed patients from Asia would have a 100% probability of developing hepatosplenic disease.[3] Taking into account the proportion of clinic patients who were from Africa (84%) and Asia (16%), this meant overall patients with disease would have a 58% probability of developing the hepatosplenic form, and 42% probability of developing the urinary form.

Probabilities of progression to various forms of active disease, given infection, were obtained from studies that reviewed the findings of consecutive autopsies in areas where schistosomiasis is endemic.[4-6] Others were obtained from clinicians' descriptions of what proportion of individuals infected with schistosomiasis go on to develop symptoms.[7-10] The probability of pyelonephritis progressing to bacteremia was obtained from a study of catheter-associated urinary tract infections.[11] For probabilistic analysis, the model assigned all progression probabilities a triangular distribution, in which the observed probability was the upper limit of the distribution, and zero was the lower limit.

The sensitivity and specificity of the serologic assay for schistosomiasis was obtained from the website of the National Reference Centre for Parasitology, which performs all the tests in Canada. [12] The probability of cure with praziquantel was obtained from the longitudinal study describe above, and modelled using a normal distribution that had the same mean and standard deviation as reported.[1]

### *Treatment pathways*

It was assumed that for certain complications of schistosomiasis, after treatment in hospital, the patient would recover with no need for follow-up in the community. This applied to: malabsorption; CNS involvement; pyelonephritis; hydronephrosis; and genital infection without secondary infertility. For patients who became infertile after a genital infection, it was assumed they would spend 4.1 years being treated. This has been reported as the mean time in treatment for Canadian couples.[13]

It was assumed the remaining complications of schistosomiasis would require community follow-up with a family doctor, and in some cases a specialist. These included: ascites; variceal hemorrhage (if the patient survived the first episode of bleeding); pulmonary hypertension; cor pulmonale; glomerulonephritis; and bladder carcinoma.

Resource use for community follow-up was estimated using published guidelines to identify what specialist consultations, medications, tests, and procedures would be required annually. It was assumed patients would require only 1 visit per year each with their family and specialist physicians. It was also assumed they would require the minimum drug therapy recommended in the management guideline. The care pathways are summarized in table 1.



Table 1) Care pathways for community follow-up of certain conditions

| **Condition** | **Annual visits** | **Medications** | **Annual Tests & Procedures*** | **Reference** |
|---|---|---|---|---|
| Bladder carcinoma | Family physician, urologist | None | CBC, electrolytes, creatinine, albumin, prothrombin time, CT pelvis | [14] |
| Ascites | Family physician, internist | Spironolactone 100 mg po daily | CBC, electrolytes | [15, 16] |
| Cor pulmonale | Family physician, cardiologist | Furosemide 60 mg po daily | (patient will already have tests ordered for pulmonary hypertension) | [17] |
| Variceal hemorrhage | Family physician, gastroenterologist | Propanolol 200 mg po daily | CBC, electrolytes, esophagogastroscopy | [18, 19] |
| Pulmonary hypertension | Family physician, respirologist | Diltiazem 480 mg po daily | CBC, electrolytes | [20] |

*CBC = complete blood count

*Costs*

The costs of hospital treatment were calculated using the Canadian Institute for Health Information (CIHI) patient cost estimator for hospitals in Alberta.[21] Because the patient cost estimator uses case mix groups, as opposed to specific diagnoses, case mix groups and their corresponding schistosomiasis complications are shown in table 2.

**Table 2) CIHI case mix groups associated with schistosomiasis complications**

| Schistosomiasis complication | CIHI Case Mix Group | Cost (patients age 18-59) |
|---|---|---|
| Pulmonary hypertension | Other lung disease | $12,706 |
| Genital schistosomiasis | Inflammatory disorder of the female reproductive system | $4,198 |
| CNS involvement | Infection/Inflammation of the CNS | $13,289 |
| Cor pulmonale | Heart failure without coronary angiogram | $11,807 |
| Malabsorption | Other gastrointestinal disorder | $5,475 |
| Variceal hemorrhage | Gastrointestinal hemorrhage | $5,714 |
| Bladder carcinoma | Malignant neoplasm of urinary system | $6,122 |
| Glomerulonephritis | Other disorder of kidney/ureter | $5,441 |
| Pyelonephritis | Upper urinary tract infection | $4,576 |
| Bacteremia | Other/unspecified sepsis | $18,122 |
| Ascites | Cirrhosis | $10, 636 |

The cost of community follow-up was calculated using the care pathways outlined in table 1 and the following costs for physician billings, medications, procedures, and tests. It was assumed family physicians would bill for complex assessments lasting 15 minutes and specialists would bill for comprehensive assessments lasting 30 minutes. Generic drug prices were used.

Table 3) Various costs used in the model

| Item | Cost | Reference |
|---|---|---|
| Family physician visit | $51.37 | [22] |
| Consult – urologist | $99.18 | [22] |
| Consult – internist | $204.39 | [22] |
| Consult – cardiologist | $127.21 | [22] |
| Consult – nephrologist | $155.83 | [22] |
| Consult – gastroenterologist | $119.96 | [22] |
| Consult – respirologist | $124.22 | [22] |
| Spironolactone 100 mg per | $0.53 | [23] |
| Propanolol 200 mg per day | $0.26 | [23] |
| Furosemide 60 mg per day | $0.11 | [23] |
| Diltiazem 480 mg per day | $0.77 | [23] |
| Complete Blood Count | $8.27 | [24] |
| Electrolytes | $7.76 | [24] |
| Creatinine | $2.59 | [24] |
| Albumin | $1.55 | [24] |
| Bilirubin | $2.59 | [24] |
| CT Pelvis | $247.60 | [25] |
| Esophagogastroscopy | $572.27 | [25] |

In a conversation May 25, 2018 David Brewerton, pharmacist at Luke`s Drug Mart in Calgary confirmed the mean dose of praziquantel prescribed to refugees seen at the MRHC clinic during 2017 was 960 mg, or 4.8 tablets. This was rounded to 5 tablets. The price his pharmacy would charge to the IFHP for 5 tabs of praziquantel was $51.19. In a conversation June 11, 2018, Joel Varsava, pharmacist at Pharmacity in Ottawa confirmed his pharmacy would charge $44.66 to the IFHP for 5 tablets. The difference in prices was due to differences in markup and dispensing fees. These two prices were treated as upper and lower limits, and the cost of praziquantel was modelled in a uniform distribution between the two.

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.

### *Survival times*

The base life expectancy used in the model was the mean life expectancy for Canadians age 36 in 2015, as reported by Statistics Canada.[26] As the mean life expectancy was 82.7 years, healthy individuals were assumed to survive for 46.7 years. Survival times with different complications of schistosomiasis were extrapolated from several studies that followed patients' survival with portal hypertension, pulmonary hypertension, cor pulmonale, glomerulonephritis, or bladder cancer.[27-31] Using Stata 15 software, different types of hazard functions (Gompertz, Exponential, Lognormal, Loglogistic and Weibull) were fit to survival study data.[32] Akaike and Bayes information criteria were used to choose which function types had the best fit to the data for each disease. The hazard functions for each disease were then extrapolated fifty years forward. For each condition, a life table was constructed by incorporating the calculated disease-specific hazard functions into the Statistics Canada life table for adult Canadians in 2015, following a method published elsewhere.[26, 33] In a given year of life, the table used either the mean Canadian risk of death, or the disease-specific risk of death, whichever was greater. Disease-specific life expectancies for patients age 36 were then obtained from each life table.

*Utilities*

Utility weights for all health states, except infertility, were calculated following the method described by Sullivan *et al*. [34] For each condition, utility decrements were subtracted from the mean utility weight (0.88) for adults age 35-49. Additional decrements were subtracted for individuals with multiple comorbid conditions. Because Sullivan *et al* do not describe disease states that precisely match different complications of schistosomiasis, states that were analogous to complications of schistosomiasis were used. The utility for infertility was obtained from a separate study.[35] These are described in table 4.

Table 4) Disease states and associated utility decrements

| Schistosomiasis complication | Analogous health state | Disutility | Standard error | Reference |
|---|---|---|---|---|
| CNS involvement | Acute cerebrovascular disease | 0.0483 | 0.0009 | [34] |
| Cor pulmonale | CHF, nonhypertensive | 0.0546 | 0.0010 | [34] |
| Malabsorption | Other gastrointestinal disorders | 0.0315 | 0.0005 | [34] |
| Variceal hemorrhage - | Gastric ulcer | 0.0269 | 0.0002 | [36] |
| Glomerulonephritis | Other diseases of the kidney | 0.0544 | 0.0011 | [34] |
| Ascites | Other liver diseases | 0.0184 | 0.0013 | [34] |
| Pulmonary hypertension | Other lung disease | 0.0428 | 0.0002 | [36] |
| Infertility | Infertility | 0.070 | - | [35] |
| Bladder carcinoma | Unspecified neoplasm | 0.0174 | 0.0001 | [36] |
| Pyelonephritis | Other diseases of the kidney | 0.0544 | 0.0011 | [34] |
| Genital schistosomiasis | Other female genital disorders | 0.015 | 0.0007 | [34] |

With the standard errors shown above, disutilities were modelled in a gamma distribution using the methods of moments.

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# Appendix 2

## External validation

The following inputs were used to approximate how many refugees settled in Calgary may have developed complications from schistosomiasis in 2017.

| Item | Estimate | Reference |
|---|---|---|
| Mean years to symptom onset | 20 | [1] |
| Mean annual immigration to Calgary 1991-2000 | 6,482 | [2] |
| Mean percent of immigrants to Calgary who were refugees 1982-2005 | 10.7% | [3] |
| Mean annual number of people diagnosed with "schistosomiasis" in discharge summaries from Calgary hospitals, 2013-2017. | 2 | see footnote (a) |
| Mean number of patients identified in physician billings for "schistosomiasis" from Calgary outpatient settings, 2013-2017. | 49 | see footnote (a) |

(a) The authors obtained data from AHS Data Integration, Management & Reporting (DIMR).

From the above figures the number of refugees who were potential MRCH patients in 1997 was estimated to be 6,482 x 10.7% = 694.

To allow for the potential for other immigrants and travellers living in Calgary to have been exposed to schistosomes, it was assumed 800 exposed individuals were in Calgary in 1997.

Allowing for 20 years until symptom onset, for the year 2017 the model predicted:

6 deaths + 62 cases with complications = 68 cases.

The mean number of schistosomiasis cases recorded by Alberta Health Services between 2013 and 2017 was:

2 inpatient cases + 49 outpatient cases = 51 cases.

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# Appendix 3

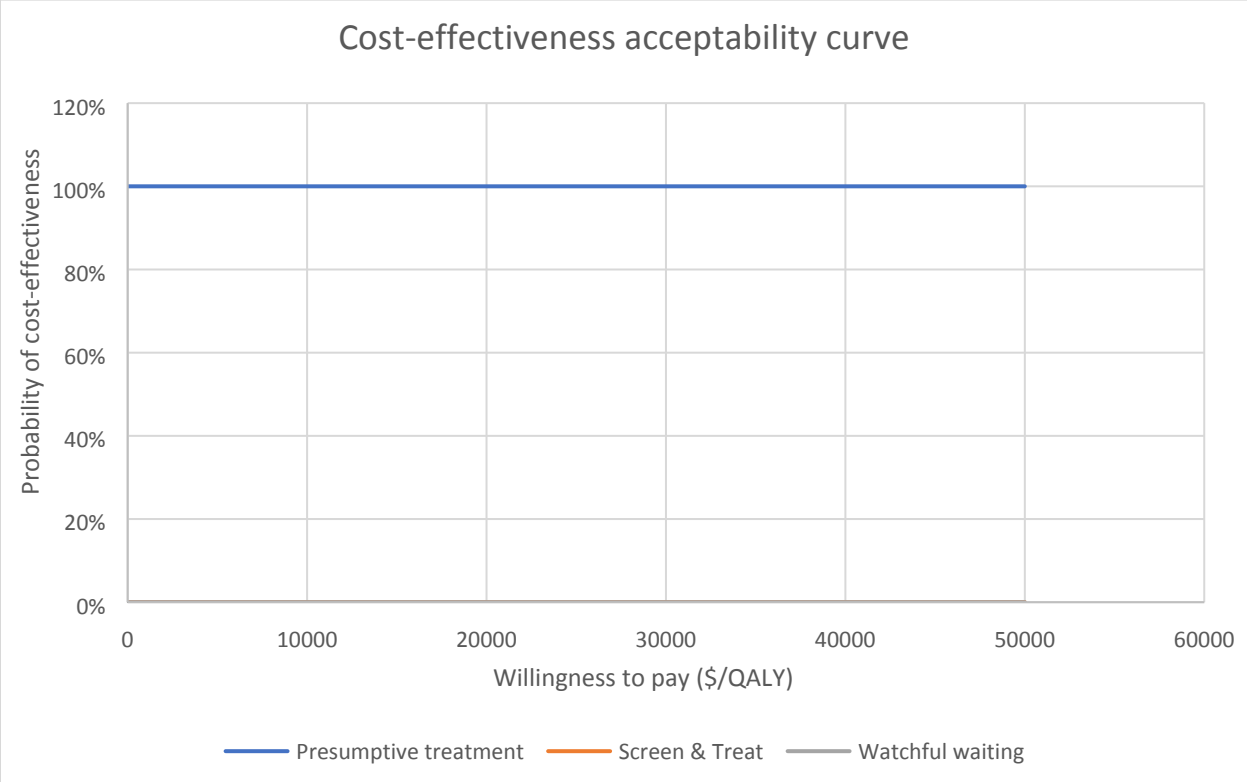
## One-way sensitivity analysis and scenario analysis

One-way sensitivity:

| Parameter | Value | Baseline | Screening & treatment vs Watchful Waiting ICER | Presumptive treatment vs Screening & treatment ICER |
|---|---|---|---|---|
| Probability of progression | ↓50% | [varies] | Dominates | Dominates |
| Probability of progression | ↓75% | [varies] | $818/QALY | Dominates |
| Onset | 35 years | [20 yrs] | Dominates | Dominates |
| Onset | 5 years | [20 yrs] | Dominates | Dominates |
| Tx cure rate | 75% | [88%] | Dominates | Dominates |
| Tx cure rate | 50% | [88%] | Dominates | Dominates |
| Community Cost | ↑100% | [varies] | Dominates | Dominates |
| Community Cost | ↓50% | [varies] | Dominates | Dominates |
| % hepatosplenic disease | 90% | [58%] | Dominates | Dominates |
| % hepatosplenic disease | 10% | [58%] | Dominates | Dominates |
| Probability die from schisto | ↑200% | [varies] | Dominates | Dominates |
| Probability die from schisto | ↓50% | [varies] | Dominates | Dominates |
| | | | | |
| Scenario: | | | | |
| Progression 50%, death prob 50%, cure rate 50% | | | Dominates | Dominates |

# Appendix 4

Probabilistic cost-effectiveness analysis



# Appendix 5

## Exploratory Analysis

Cost vs Prevalence

To find the prevalence at which the cost of presumptive treatment equals the cost of watchful waiting, first we use the results of the linear regression to write the equations of the regression lines for presumptive treatment and watchful waiting.

Presumptive treatment: Cost = -3.555571*Prevalence - 45.5405

Watchful waiting: Cost = -22.38904*Prevalence - 0.0385879

Then we make the two functions equal and solve for Prevalence.

Let:

-3.555571*Prevalence - 45.5405 = -22.38904*Prevalence - 0.0385879

Prevalence = (45.5405 - 0.0385879) / (22.38904-3.555571)

= 2.416013327 %

NMB vs Prevalence

We can use the same method to find the prevalence at which net monetary benefit is equal for presumptive treatment and watchful waiting.

Presumptive treatment: NMB = -372.5566*Prevalence + 1499454

Watchful waiting: NMB = -727.5113*Prevalence + 1499500

Let:

-372.5566*Prevalence + 1499454 = -727.5113*Prevalence + 1499500

Prevalence = (1499500 – 1499454) / (727.5113-372.5566)

= 0.129594002 %