2019-01-14

Cost-effectiveness of screening and treatment for schistosomiasis among refugees coming to Canada

Webb, John Angus

UNIVERSITY OF CALGARY

Cost-effectiveness of screening and treatment for schistosomiasis among refugees coming to Canada

by

John Angus Webb

A THESIS

SUBMITTED TO THE FACULTY OF GRADUATE STUDIES

IN PARTIAL FULFILMENT OF THE REQUIREMENTS FOR THE

DEGREE OF MASTER OF SCIENCE

GRADUATE PROGRAM IN COMMUNITY HEALTH SCIENCES

CALGARY, ALBERTA

JANUARY, 2019

Abstract

Background

Depending on their countries of origin, between 12% and 73% of resettled refugees and asylum seekers from endemic countries are infected with schistosomiasis when they arrive in Canada. Many are asymptomatic, but they are at risk for complications that may develop decades later. In Canada, clinicians previously practiced watchful waiting, treating patients if they developed symptoms; but in 2011 new guidelines recommended screening and treatment instead. In the United States, refugees from Africa are presumptively treated for schistosomiasis before they leave their country of origin. The cost-effectiveness of screening or presumptive treatment for schistosomiasis has never been studied.

Methods

We constructed a decision-tree model to examine the cost-effectiveness of three management strategies: watchful waiting; screening and treatment; and presumptive treatment. We obtained model data from the literature and other sources, predicting deaths and chronic complications caused by schistosomiasis; as well as costs, and net monetary benefit.

Results

Presumptive treatment was cost-saving if the prevalence of schistosomiasis in the target population was greater than 2.4%. In our base case analysis, presumptive treatment was associated with an increase of 0.15 quality-adjusted life years and a cost savings of $383 per person, compared to watchful waiting. It was also more effective and less costly than screening and treatment.

Interpretation

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 with prevalence greater than 2.4%. Our results support a revision of the current Canadian guidelines.

Table of contents

List of Tables

List of Figures

List of abbreviations

AHS	Alberta Health Services
ASID	Australasian Society for Infectious Diseases
CADTH	Canadian Agency for Drugs and Technology in Health
CCIRH	Canadian Coalition for Immigrant and Refugee Health
CDC	Centers for Disease Control
CIHI	Canadian Institute for Health Information
CNS	Central Nervous System
DALY	Disability-Adjusted Life Year
G-ELISA	Immunoglobulin G Enzyme-Linked Immunosorbent Assay
ICER	Incremental Cost-Effectiveness Ratio
IFHP	Interim Federal Health Program
MRHC	Mosaic Refugee Health Clinic
NMB	Net Monetary Benefit
NRCP	National Reference Centre for Parasitology
PCT	Preventive Chemotherapy
QALY	Quality-Adjust Life Year
WHO	World Health Organization
WTP	Willingness to Pay

Chapter 1

Schistosomiasis

Background

Schistosomiasis

Schistosomiasis is a major cause of chronic disease throughout sub-Saharan Africa, as well as parts of Asia, the Middle-East, South America and the Caribbean.(1) It is contracted through exposure to contaminated water, typically where it is necessary for people to bathe or perform chores in lakes, streams or rivers. Schistosomes are naturally occurring freshwater parasites. In the water, they penetrate the skin, migrate into the circulatory system, and secrete eggs into the bloodstream. This secretion continues throughout the parasite's lifetime. Its eggs travel to different organs, where they cause inflammation and fibrosis. Different species of schistosome primarily affect either the urinary tract, or the intestines, liver, and spleen. The latter form is sometimes known as hepatosplenic disease. Over time, urinary or hepatosplenic disease can also affect the lungs, kidneys, female reproductive tract, and uncommonly the central nervous system(CNS) or other organs. Urinary disease is also a risk factor for carcinoma of the bladder.(2-8)

Schistosomiasis in non-endemic areas

To infect humans, schistosomes require an intermediate host: freshwater snails. Appropriate species of snails are not found in Europe or North America, with the exception of the Caribbean.(9, 10) Hence, all reported cases of schistosomiasis in Canada result from travel to or immigration from endemic areas. (11-15) Tourists who are briefly exposed while abroad are likely to develop an acute infection that can resolve spontaneously or be treated effectively with medication.(16, 17) However, immigrants or refugees who have been in routine contact

with contaminated water throughout their lives may develop chronic schistosomiasis.(18) An unusually high prevalence of schistosomiasis has been observed in some refugee populations.(19) This may be the combined result of poor access to health care, and spending extended periods of time in refugee camps with inadequate sanitation.(20, 21).

Practice guidelines

In 2011 the Canadian Collaboration on Immigrant and Refugee Health (CCIRH) recommended all refugees coming to Canada from Africa be screened and treated for schistosomiasis.(22) 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.(23) In the United States, the Centers for Disease Control (CDC) recommend all refugees from endemic countries be presumptively treated for schistosomiasis (which is to say, without being tested) prior to departure for the US.(24)

Guideline implementation

Most Canadian refugee health centres and family physicians have implemented the CCIRH guideline, though not all.(25) 'Watchful waiting', or identifying disease when patients develop symptoms, is still practiced. Although a number of factors likely underpin the limited uptake of these contemporary guidelines, one reason may be the CCIRH's acknowledgement of a lack of evidence that screening in a non-endemic country improves health outcomes.(22)

Economic Evaluation

Given this uncertainty, clinicians and funding agencies may benefit from information about what costs and benefits are involved in screening for schistosomiasis, compared to

watchful waiting. Furthermore, it's unclear whether presumptive treatment, as practiced in the US, could also be cost-effective. A cost-utility analysis can compare all three options in terms of the health benefits, and costs or potential savings associated with each.

Cost-utility analysis is one type of economic evaluation. Cost-benefit, cost-minimization, cost-consequence and cost-effectiveness studies are the other common types.(26) All of them involve comparing the costs and consequences of at least two alternatives, however each quantifies consequences differently. Cost-benefit analysis converts all consequences to a single dollar value. (26) Cost-consequence analysis expresses consequences as a group of related but heterogeneous outcomes. (26) Cost-minimization assumes the consequences of various alternatives are the same, and focuses on which is less expensive. (26)

Cost-utility analysis is closely related to, but differs from, cost-effectiveness analysis. Cost-effectiveness analysis can be conducted using any outcome of an intervention, such as an increase in years of life. However, such 'natural units' can be difficult to compare across interventions. For example: if one intervention leads to increased years of life, and another leads to reduction in pain, their outcomes cannot be compared. Cost-utility analysis facilitates comparison between such interventions, because it converts all outcomes to the common denominator of utility. Utility preferences can be derived in several different ways, one of which is to calculate preference-based scores. This involves using a generic survey to assess how strongly patients 'prefer' to be in a given health state. (26)

Cost-utility analysis grew out of cost-effectiveness analysis, and as a result some authors prefer not to make a distinction between them.(26) Interchangeable use of cost-utility and cost-effectiveness can be confusing, but it occurs in the literature nonetheless.

Review of the literature

Burden of disease

Endemic areas

Globally, the World Health Organization (WHO) estimates schistosomiasis causes the loss of 4.5-million disability-adjusted life years (DALYs) per year; which is more than trachoma, leishmaniasis, Chagas disease or infectious hepatitis.(27) The greatest proportion of morbidity and mortality, 3.5-million DALYs, occurs in Sub-Saharan Africa. The WHO estimates 85% of individuals who require treatment for Schistosomiasis live in Africa.(1, 27)

Detailed descriptions of morbidity in certain populations can be found in several autopsy and field studies.(28-40) These are discussed further in Appendix 1.

Non-endemic areas

Estimates of the burden of disease in Canada and the United States are limited to studies of prevalence of infection among asymptomatic immigrants and refugees, which ranges from 12% to 73%, depending on the population studied.(15, 28, 41-46) Schistosomiasis is not a reportable disease in Canada or the United States and there are no published estimates of associated morbidity or mortality. In the past, schistosomiasis was characterized as a disease of minor concern in North America. For example, in 1999 one US-based researcher excluded schistosomiasis from a major study on parasitic infections, because New York State discharge

and billing data suggested schistosomiasis caused a “negligible” number of hospital admissions.(47)

Concern about schistosomiasis in refugees to North America increased in 2004, when the CDC responded to a cluster of unexplained abdominal pain among Sudanese and Somali immigrants. It found up to 73% were infected with Schistosomiasis, and recommended presumptive treatment of immigrants from endemic areas.(41) Because of the relative unavailability of serologic testing in the United States, the CDC recommended foregoing testing, and presumptively treating immigrants and refugees before departure. It was assumed this would be cost-effective, because presumptive overseas treatment for another parasite, strongyloides, had already been found cost-effective.(41, 47) Furthermore, the first-line treatment for schistosomiasis (praziquantel) is available in a generic form in many developing countries, and costs less than in North America. This may be why the recommendation for presumptive treatment of schistosomiasis was made without a full economic evaluation. There is limited evidence of effectiveness. After overseas presumptive treatment began, one study noted a 2.3% decrease in the frequency of helminth infections, including schistosomiasis, among refugees coming to California.(48)

Cost-effectiveness of existing schistosomiasis programs

A small number of evaluations have explored economic aspects of schistosomiasis control programs in endemic areas, for example: comparing the cost per symptomatic patient treated with praziquantel, using different criteria for treatment, in Burundi(49); estimating the QALYs gained through different national control programs in Kenya(50); and estimating the total cost to society, by continent(51). Studies by Muennig *et al,* Anderson & Moser, and

Maskery *et al* have shown presumptive treatment of immigrants to the United States for parasitic disease other than schistosomiasis are cost-effective.(52-54) When the CDC first recommended adding presumptive treatment for schistosomiasis, they assumed cost-effectiveness, based on the studies for other parasites.(41) However, there has never been a full economic evaluation that measures costs and consequences of screening and treatment, or presumptive treatment of schistosomiasis; nor has there been an evaluation of programs for immigrants or refugees in their receiving country.

Effectiveness of testing

In Canada, testing for schistosomiasis is typically performed by serology sent to the National Reference Centre for Parasitology (NRCP) in Montreal. The NRCP uses an IgG Enzyme-Linked Immunosorbent Assay (G-ELISA) that detects antibodies against schistosomes, and has been benchmarked against known blood samples from the Centres for Disease Control (CDC) in Atlanta.(13) The G-ELISA is considered 90% sensitive and 99% specific for schistosomiasis.(55) Some false positives occur because the individuals tested come from communities that have mass treatment programs, and antibodies persist in individuals who have been successfully treated. The assay does not identify individual species of schistosome and may not detect species that are less common.

Effectiveness of treatment

Praziquantel has been the recommended treatment for schistosomiasis since the 1970s. It is taken in one to three doses over the course of a single day. A recent Cochrane review

found, in populations where the prevalence of schistosomiasis is less than 30%, a one-day course of Praziquantel achieves cure rates between 81% and 95%.(56)

The Cochrane review focuses on populations in areas where schistosomiasis is endemic and exposure has been recent. But calculated estimates of how long schistosomes survive in the human body, without re-exposure, range from 3 to 37 years. (57,58) It appears that antiparasitic medication continues to be effective for decades after exposure.(59) There have been several case reports of complications that emerge years to decades after exposure. One case series describes 10 refugees from the second world war who emigrated from camps in East Africa to Australia during the 1950s. Two to three decades later, they developed various symptoms of chronic schistosomiasis. Their illnesses all responded to treatment with praziquantel. (59) Two other case studies describe Brazilians who presented to care with thyroid and pulmonary nodules at least 25 years after being exposed to schistosomes. Both patients' symptoms resolved after treatment with praziquantel or another antiparasitic, oxamniquine. (60, 61) In a thirteenth case, pulmonary nodules containing schistosome eggs were eliminated entirely after treatment with praziquantel 16 months following exposure. (62) The author is not aware of any case reports that describe treatment failure for people with chronic complications of schistosomiasis.

Objectives and methods overview

This study addresses whether, from the Canadian publicly-funded health care payer perspective, screening, and treatment of schistosomiasis among newly-arrived refugees is cost-effective, compared to watchful waiting. It also addresses whether implementing presumptive

treatment of all patients (without screening) would be cost-effective, compared to screening and treatment.

Primary outcome

The primary outcome was the incremental cost-effectiveness ratio (ICER) for each of two comparisons: (1) screening and treatment compared to watchful waiting; and (2) presumptive treatment compared to screening and treatment. The ICER was expressed as an incremental cost per quality-adjusted life year ($/QALY) using the formula: ICER = $(cost_1 – cost_2) \div (utility_1 – utility_2)$.

Utility was calculated as the product of the time spent in a particular health state, and a utility preference associated with that health state. Utility preferences can be derived in several different ways, one of which is to calculate preference-based scores. This involves using a generic survey to assess how strongly patients 'prefer' to be in a given health state. (26) Utility preferences used in this study were derived by analysis of scores on a generic survey instrument, the Euroquol EQ-5D. (63) Those scores were associated with different conditions using clinical classification categories developed by the American Agency for Healthcare Research and Quality for different chronic diseases.(63)

Uncertainty

Uncertainty was explored using a Monte Carlo simulation, one-way sensitivity analyses, scenario analysis and a decision curve. In the Monte Carlo simulation disease progression probabilities, costs and utilities were allowed to vary simultaneously according to pre-specified distributions.

A probabilistic ICER was calculated and a probabilistic sensitivity analysis was conducted. Disease progression probabilities were modelled using triangular distributions, in which the progression probabilities found in the literature are both the upper limits and modes. This reflects an assumption the probabilities of progression in a non-endemic country such as Canada are likely to be lower than in endemic countries, since there is no ongoing exposure to contaminated water in non-endemic countries. Costs other than drug prices and laboratory fees were modelled using gamma distributions. The period of illness onset was modelled in a normal distribution between 1 and 40 years after emigration at a mean age of 36 (which assumes exposure by the age of 20 and symptom onset 16 to 56 years later). The study employed a lifetime analytic time horizon.

One-way sensitivity analyses assessed the model's sensitivity to variables including, but not limited to: disease prevalence; drug and testing costs; rates of patient acceptance of screening and treatment; treatment failure rate; and disease progression rates.

A decision curve was used to model the net monetary benefit (NMB) of each option as a function of disease prevalence, in order to illustrate how cost-effectiveness varied with prevalence. Net Monetary Benefit was calculated 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 the conventional willingness-to-pay threshold of $50,000 per QALY. For a given level of disease prevalence, whichever option has the greatest NMB was considered cost-effective.

A scenario analysis modelled cost-utility under the assumption that a generic form of praziquantel has entered the Canadian market. (Generic manufacturer has become a theoretical possibility since the drug's Canadian patent protection expired in 2016.) The scenario analysis assumed the cost of praziquantel is 18% of its current market price, in accordance with the Alberta government's policy on generic pricing.(64)

Uncertainty surrounding utility coefficients was modelled by calculating decrements assigned a gamma distribution (where utility = 0.88 – decrement).(65) Uncertainties in life expectancy were modelled by using alternative (i.e. Gompertz, log-logistic, log-normal, and exponential) distributions to estimate annual death rates.(66)

Equity

It was assumed in this study that all quality-adjusted life years were equal. Although the target population, recently arrived refugees, may face unique social, economic and health challenges: these will not be considered in the analysis. An argument could be made for either weighting QALYs experienced by the target population more heavily, or using a higher willingness-to-pay threshold than the typical $50,000/QALY. In order to strengthen the conclusions of the study,this was not be done. Assuming QALYs experienced by a member of the target population are equal to those experienced by the general populace biases the results of the study toward the null; since gains of losses experienced by members of the target population will be valued no more than they are for members of the general public.

Chapter 2

The cost-effectiveness of schistosomiasis screening and treatment among recently resettled refugees to Canada

Introduction

Schistosomiasis, or infection with schistosomes, is a relatively unknown disease in North America, Europe and Australia. 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.(4)

Refugees are disproportionately affected due to poor access to safe water and health care prior to resettlement.(21) They may be asymptomatic when they arrive in their new country, but 12%- 73% have latent infection.(15, 19) 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.(4)

In 2011 the Canadian Collaboration for Immigrant and Refugee Health (CCIRH) recommended screening and treatment for refugees from Africa for schistosomiasis.(22) 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.(23) In the United States, the Centers for Disease Control (CDC) has a policy to presumptively treat for schistosomiasis before refugees leave Africa.(24)

A structured review of the literature identified three studies that evaluated the cost-effectiveness of programs that presumptively treated refugees, coming from endemic areas to a non-endemic country, for intestinal parasites: but schistosomiasis was not among the parasitic diseases those programs treated.(53-55) We identified one study that evaluated the relative costs of screening and treatment compared to presumptive treatment for refugees; however it was published before serologic testing was available, and it did not include the costs or consequences associated with chronic complications of schistosomiasis.(67) Yet the number of displaced persons worldwide is at its highest level since the United Nations High Council of Refugees was created.(68) 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 of 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 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, to increase the generalizability of our results we used a prevalence range of 0-30% in a subsequent exploratory analysis. (Although the prevalence could in theory be higher in some Canadian settings, this range proved sufficient to explore how cost-effectiveness relates to prevalence.)

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%.(57) It is well tolerated though some patients experience minor and transient side effects including: gastrointestinal symptoms, nausea, fatigue and dizziness.(69) 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. (4) 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%.

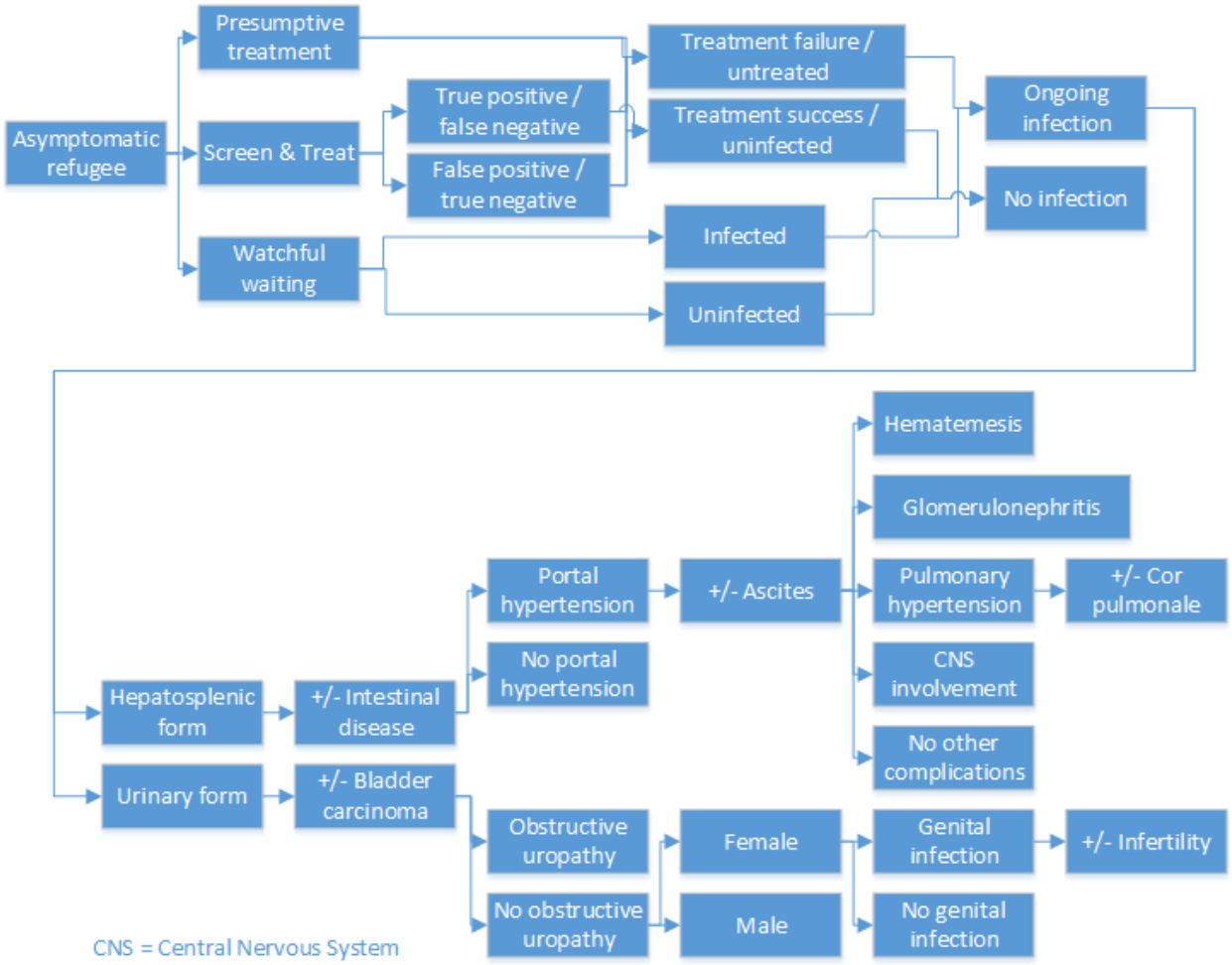
Presumptive treatment

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. 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 for those who died from complications of schistosomiasis.



Model parameters

The model assumed patients would present to care when they became symptomatic, typically with one presenting problem. However it was assumed comorbid intestinal disease and/or ascites could be present with other hepatosplenic complications. Complications of urinary disease could occur simultaneously with cancer of the bladder and/or infertility in females. 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.(70) 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.(71) Costs of hospital-based care were estimated using the Canadian Institute for Health Information (CIHI) Patient Cost Estimator.(72) We estimated community care costs by using the Alberta Health Care Insurance Plan schedules of medical and drug benefits to estimate the cost of managing specific complications according to published guidelines (see Appendix 1).

Refugee claimants and protected persons, including resettled refugees, 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.(73) 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.)

Table 1) Model parameters

Parameter	**Value**	**Range**	**Reference**
Mean age of patients (yrs)	35.9	-	Unpublished data

Age of symptom onset (yrs)	55	36 - 84	(18)
probability of patient being female	0.487	-	Unpublished data
probability of patient being infected	0.232	0.181 - 0.293	Unpublished data
probability of test being (+) given presence of infection	0.99	-	(56)
probability of test being (-) given absence of infection	0.90	-	(56)
probability of patient consenting to screening test	0.98	-	See footnote (a)
probability of patient accepting treatment given (+) test result	0.98	-	See footnote (a)
probability of patient being cured by treatment	0.88	0.799 - .929	(18, 57)
probability of hepatosplenic (vs. urinary) involvement, given infection	0.45	-	Unpublished data
probability of urinary obstruction, given infection	0.287	0 - 0.431	See Appendix 1
probability of hydronephrosis, given infection	0.228	0 – 0.342	See Appendix 1
probability of pyelonephritis, given obstruction	0.197	0 - 0.295	See Appendix 1
probability of bacteremia, given pyelonephritis	0.143	0 – 0.341	See Appendix 1
probability of genital disease, given infection in female	0.333	0 – 0.500	See Appendix 1
probability of carcinoma, given infection	0.027	0 - 0.041	See Appendix 1
probability of intestinal disease, given infection	0.133	0 - 0.200	See Appendix 1
probability of portal fibrosis, given infection	0.139	0 - 0.209	See Appendix 1
probability of ascites, given fibrosis	0.070	0.010 - 0.100	See Appendix 1
probability of hematemesis, given fibrosis	0.027	0 - 0.040	See Appendix 1
probability of death, given hematemesis	0.153	0 - 0.230	See Appendix 1
probability of pulmonary hypertension, given fibrosis	0.186	0 - 0.230	See Appendix 1
probability of cor pulmonale, given fibrosis	0.050	0 - 0.075	See Appendix 1
probability of glomerulonephritis, given fibrosis	0.067	0 - 0.100	See Appendix 1
probability of CNS involvement, given infection	0.001	0 - 0.002	See Appendix 1
Survival if no schistosomiasis complications (yrs)	28.9	-	(74)
Mean survival for glomerulonephritis (yrs)	17.3	-	See Appendix 1
Mean survival for pulmonary hypertension (yrs)	9.4	-	See Appendix 1
Mean survival for bladder cancer (yrs)	5.3	-	See Appendix 1
Mean survival for cor pulmonale (yrs)	7.0	-	See Appendix 1
Mean survival for portal hypertension (yrs)	27.8	-	See Appendix 1
Years of treatment for infertility	4.1	-	(75)
Utility discount rate (%)	1.5	-	(76)
Cost discount rate (%)	1.5	-	(76)
Mean dose of praziquantel (mg)	1000	-	See footnote (b)
Cost of praziquantel ($)	47.93	44.66 – 51.19	See footnote (b)
Cost of serology ($)	74.09	61.21 - 86.97	See 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	See Appendix 1
CNS involvement	$13,289	$0	0	-	See Appendix 1
Cor pulmonale	$11,087	$560	0.055	0.052 - 0.058	See Appendix 1
Glomerulonephritis	$5,441	$163	0.054	0.051 – 0.058	See Appendix 1
Variceal hemorrhage	$5,714	$440	0	-	See Appendix 1
Intestinal malabsorption	$4,441	$0	0	-	See Appendix 1
Pulmonary hypertension	$12,706	$235	0.043	0.042 – 0.043	See Appendix 1
Bladder carcinoma	$6,122	$362	0.017	0.017 – 0.018	See Appendix 1
Genital schistosomiasis	$4,198	$0	0	-	See Appendix 1
Infertility	$0	$674	0.070	0.067 – 0.073	See Appendix 1
Pyelonephritis	$4,576	$0	0	-	See Appendix 1
Bacteremia	$18,122	$0	0	-	See Appendix 1
Hydronephrosis	$5,441	$0	0	-	See Appendix 1
Two comorbities	-	-	0.091	0.090 – 0.092	See Appendix 1
Three comorbities	-	-	0.084	0.082 – 0.086	See Appendix 1
Baseline health state	-	-	0.120	-	See Appendix 1

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.) Whichever option had the greatest NMB at a given disease prevalence was considered cost-effective at that prevalence. In order to determine the prevalence at which one strategy became cost-effective relative to another, we used Stata 15 to conduct linear regression of NMB against prevalence and plot linear functions of NMB versus 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 lifetime analytic horizson. Future costs and benefits were discounted at 1·5% annually, in keeping with the Canadian Agency for Drugs and Technologies in Health (CADTH) guidelines.(76)

Sensitivity Analysis

We performed both one-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

Internal validation of the model consisted of verifying patients with disease had shorter mean life expectancy, lower mean utility, and higher mean cost of care than patients without disease. Similarly, we confirmed by inspection that relative severe complications of schistosomiasis were associated with lower life expectancy and utility and higher cost of care than less severe complications.

To externally validate 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 base case 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 two 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 one death and seven cases of complications per 1000 patients.

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

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.

Figure 2a) NMB vs. Prevalence (regression lines shown)

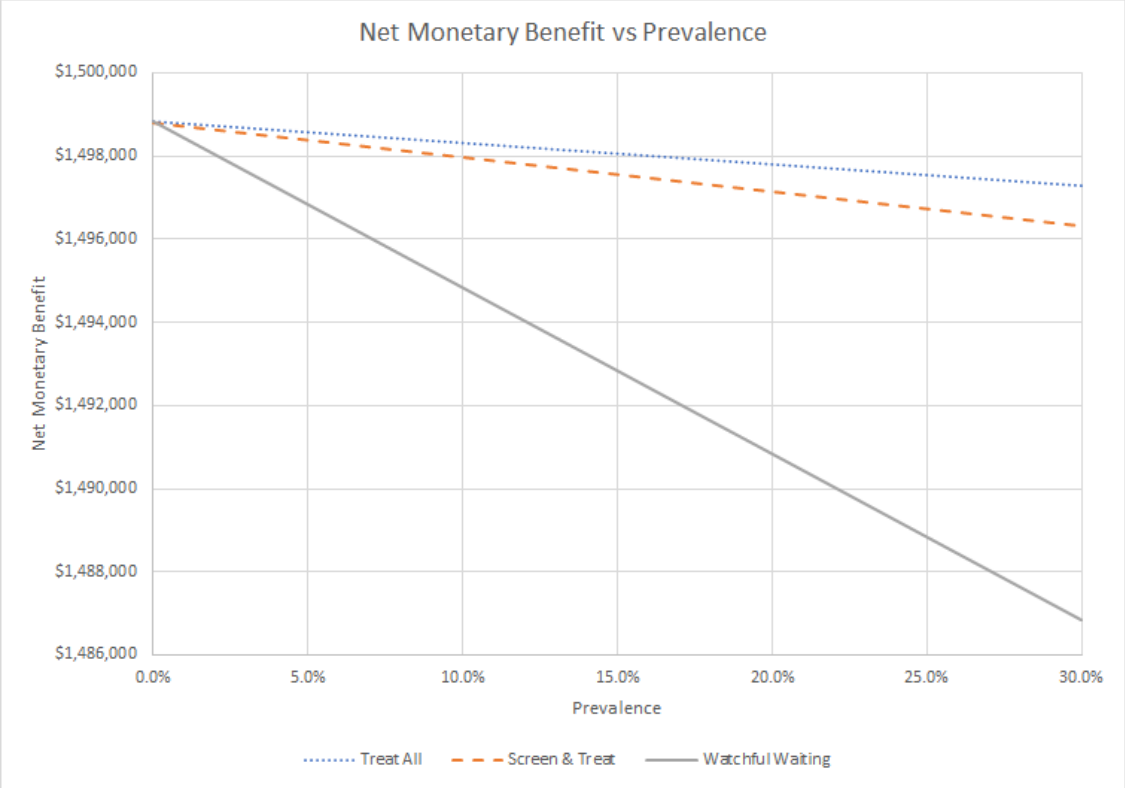


Figure 2b) Detail of figure 2a. Scale expanded to show where regression lines intersect

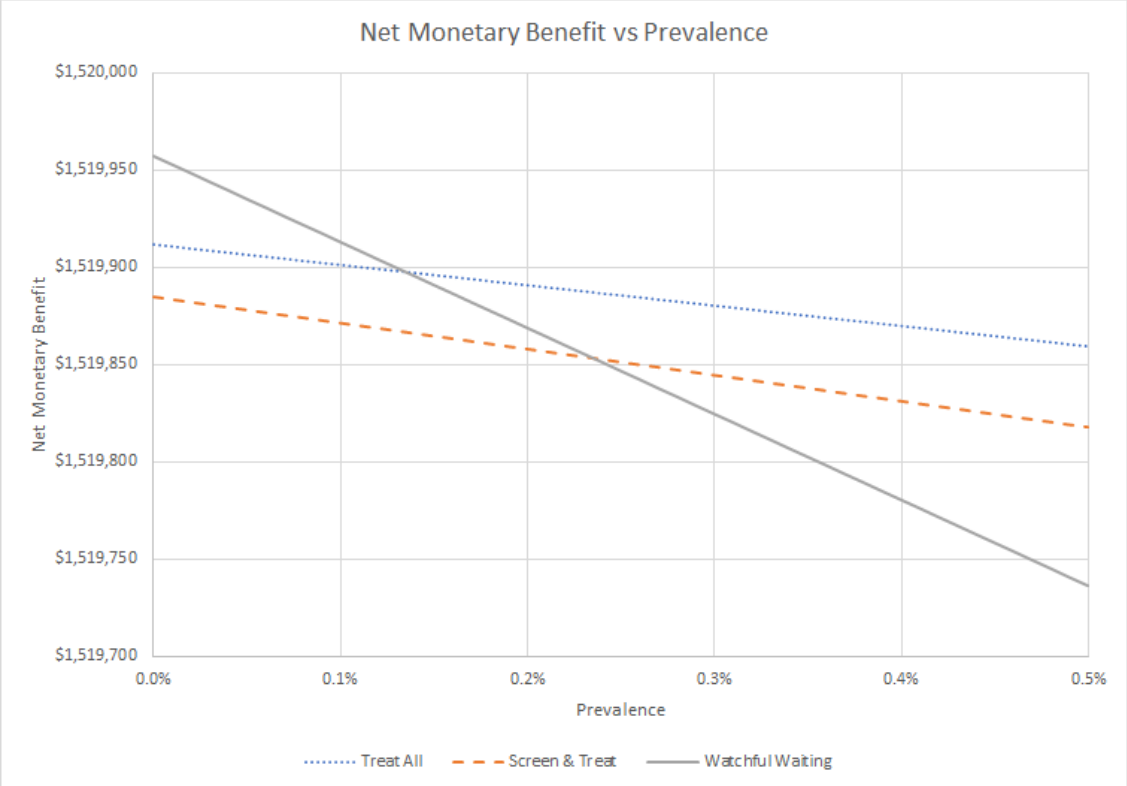
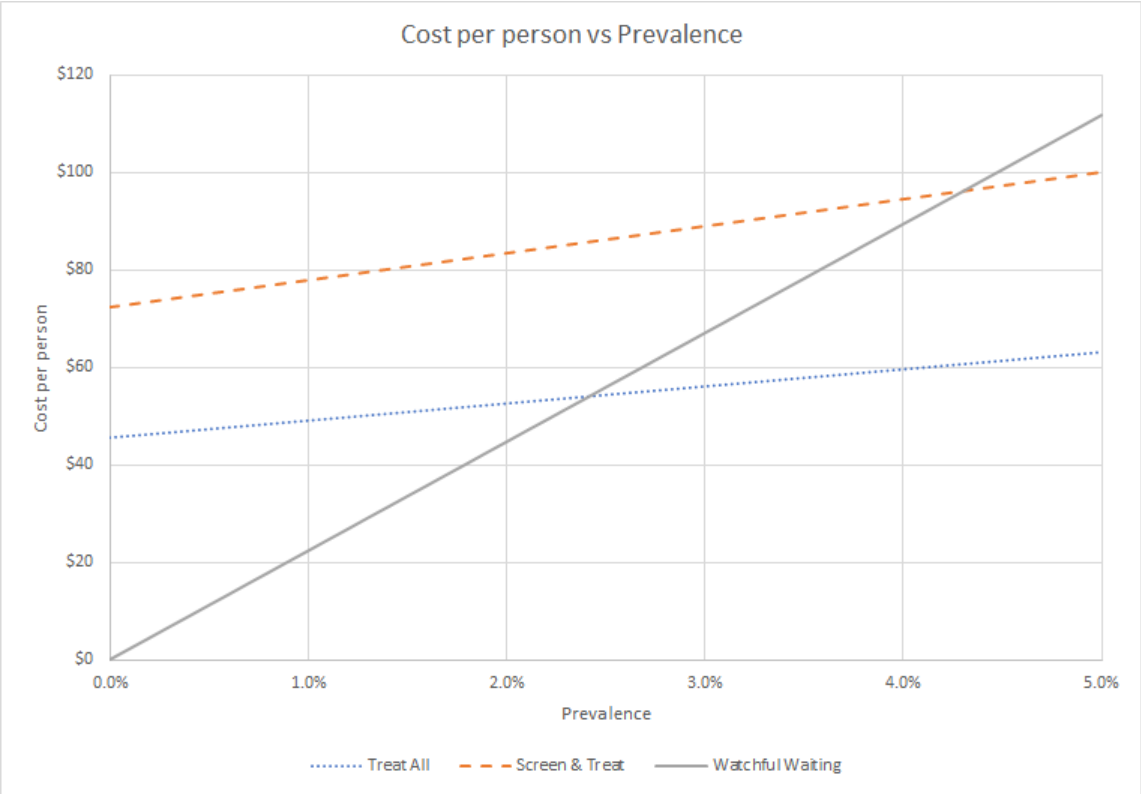


Figure 3) Cost per person, by strategy, as a function of prevalence.



Discussion

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 refugee health care.

Studies by Muennig *et al,* Anderson & Moser, and Maskery *et al* have shown presumptive treatment of immigrants to the United States for parasitic disease other than schistosomiasis are cost-effective.(53-55) When the CDC first recommended adding presumptive treatment for schistosomiasis, they assumed cost-effectiveness, based on the studies for other parasites.(42) After presumptive treatment for schistosomiasis began, a follow-up study observed a decrease in schistosomiasis among refugees coming to California.(49) Ours is the first study to provide evidence the CDC's recommended practice is cost-effective and likely cost-saving.

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 is 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**.** Figure 3 shows presumptive treatment is less costly than screening and treatment at any prevalence greater than zero, because a prescription for praziquantel costs the health care system a few dollars less than laboratory testing. The difference widens with increasing prevalence, because presumptive treatment prevents complications in cases that would be missed under screening and treatment due to occasional false negative screening test. Presumptive treatment is also 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 in place of 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. There are three potential explanations for this including: under-recognition of this infection in a non-endemic setting, potential for co-infection with other infections (e.g. Hepatitis B) that complications will be attributed to, and the inaccuracies of billing data due to coding errors. 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 model also required patients to be assigned to only one form of the disease (hepatosplenic versus GU), but it is probable that many patients are infected with both forms.

Increasing the complexity of disease would increase the cost of long-term follow-up and decrease health; therefore the simpler approach taken has the effect of underestimating the benefit of presumptive treatment. 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. These conclusions do not depend on prevalence, as long as the cost of treatment remains less than that of testing. If the cost of praziquantel were to increase, or the cost of serology were to decrease sufficiently, testing and treatment could become cost-effective relative to presumptive treatment for populations with lower prevalence.

Chapter 3

Implementation of the Results

This chapter explores how to apply the conclusions in Chapter 2, first to medical practice, then to funding and policy. It ends with some general conclusions about the value of performing a full economic evaluation.

Considerations for practice

For a medical practitioner, a key question may be whether the results of this study apply to their refugee patients. The study found presumptive treatment would be cost effective if the prevalence in the patient population was more than 0.13 percent. Hypothetically, there may be some practices where the prevalence among potentially exposed patients is lower; but it would be impractical for physicians to consider that question. The model, and the 0.13% threshold are naturally subject to error. The threshold can be interpreted to mean presumptive treatment is cost-effective if schistosomiasis prevalence is more than zero. So, the answer for the practitioner is: treat patients if there is a reasonable probability they have been exposed, and evidence of at least some disease in the community.

This means practitioners need a practical method of deciding which groups of patients were likely exposed, in their countries of origin. Since practitioners know what country their patients are from, ideally they would be able to look up the prevalence in a patient's home country and decide whether to treat. But epidemiologic data for schistosomiasis are often unavailable, due to a lack of public health infrastructure in endemic countries. The World Health Organization (WHO) published a detailed Global Schistosomiasis Atlas in 1987.(77) It provides a community-by-community description of where schistosomiasis is present, but no data on prevalence. It has never been updated. Instead, the WHO now offers an online

resource, the Global PCT (Preventive Chemotherapy) Databank.(78) The creators of the databank acknowledge the lack of epidemiologic data meant they had to find a measure other than prevalence to describe variation in risk between countries. (79) Therefore, they simply classify countries as: “non-endemic”; “interruption of transmission to be confirmed”; or “requiring preventive chemotherapy”. The latter category denotes countries for which the WHO recommends preventive treatment for the general population. As of 2016, the countries requiring preventive chemotherapy were: Egypt and all sub-Saharan Africa countries; China, Laos and Cambodia; Indonesia and the Philippines; Brazil and Venezuela.(78) Some doctors may be able to refer to this list when deciding which patients to treat, or develop a workplace protocol for recommending presumptive treatment. A simpler, if less specific approach might be: presumptively treat patients from Africa, Asia, and South America.

Extending this logic further, it may be cost-effective for physicians to offer presumptive treatment (or screening) to non-refugees who have emigrated from the above countries, as well as returning travellers, if they were exposed to fresh water. Although the prevalence among them might not be as high as 20%, it could easily be higher than the 0.24% threshold above which both presumptive treatment and screening and treatment are cost-effective, relative to watchful waiting. Although presumptive treatment costs the health care system less, immigrants and returning travellers might prefer to be screened first, because their cost for praziquantel would not be covered by the IFHP.

Considerations for funders

If a significant proportion of health care providers began to presumptively treat schistosomiasis, it's interesting to consider whether they might encounter any structural barriers. Viewed from a bird's eye perspective that inclues the entire health care system, presumptive treatment is the least costly and most effective method of preventing schistosomiasis complications among refugees. But the system is composed of multiple programs, and if a specific program bore all the costs but none of the savings, it might prefer a different option.

In Canada, depending on one's location, the status quo is either watchful waiting or screening and treatment. The different costs involved are paid by several different organizations, including: Health Canada (which pays some of the cost of testing at the National Reference Centre for Parasitology); provincial ministries of health (which fund health care services); as well as specialized clinics and individual physicians (who pay user fees for tests). If they have a prescription, refugees' and asylum claimants' purchases of praziquantel are paid for by Immigration, Citizenship and Refugees Canada, through the Interim Federal Health Program (IFHP).

We may consider what would happen if the Canadian Coalition for Refugee and Immigrant Health (CCIRH) changed its recommendation for African refugees from schistosomiasis screening to presumptive treatment. According to the Immigration and Refugee Board, in recent years an average of 6,484 refugee claimants have arrived in Canada from Africa annually.(80) If claimants were treated with a mean dose of 1000 mg of praziquantel (which

sells for approximately 50 dollars) the cost to the IFHP would be approximately 320,000 dollars. This is a small amount in comparison to the IFHP's total budget. The 2017 federal budget allotted it 78 million dollars, of which it spent 74 million.(81) Assuming the same level of need, reimbursing the prescriptions required for presumptive treatment of schistosomiasis would require a 0.4% increase in IFHP spending, which it could conceivably afford.

But the budget of the IFHP has been a political issue in recent history (82). If there were concerns about increased costs for the IFHP, it would not ease concerns to know the savings from presumptive treatment would be in programs outside the federal government. The savings would accrue to the National Reference Centre for Parasitology, which performs testing, and provincial health care plans, which pay for the health care of refugees after their claims are approved.

The NRCP would consume fewer resources because with a shift to presumptive treatment, there would be less demand for schistosomiasis serology. The NRCP currently offers schistosomiasis testing at a financial loss of undetermined magnitude. In a conversation February 1, 2018 the Laboratory Director, Dr. Momar Ndao described the funding of the schistosomiasis test as follows: Health Canada gives the laboratory block funding to support testing refugees for schistosomiasis and six other parasites (including strongyloides). This funding does not fully cover the cost of the tests, so the lab charges a 'cost recovery' fee of 30 dollars for strongyloides, while schistosomiasis is offered at no charge. (Physicians generally order both tests at the same time, following the CCIRH guideline.) We may speculate on what would happen if demand for schistosomiasis testing fell. The Health Canada funding would likely need to remain at the same level, which is less than the NRCP spends to offer the full

complement of tests. Presumably, the savings from less use of lab resources would be shared by the NRCP's two other funding agencies: the McGill Centre for Tropical Diseases and the Montreal General Hospital.(83)

In time, further savings would accrue to provincial health agencies. In chapter 2, we estimated presumptive treatment would save up to $389 per refugee in Alberta every year (allowing for the likelihood watchful waiting is performed in some areas, and screening in others). It would take approximately 20 years for the effects of prevention to be fully realized in the health care system. If we assume the doctors at the Mosaic Refugee Health Centre in Calgary presumptively treated 1000 new patients per year, it would save Alberta Health approximately 380 thousand dollars annually, discounted to present-day values. This would constitute a miniscule reduction in the 15.2 billion dollars the province now spends every year on health care: equal to less than one one-thousandth of a percent. The savings may not be noticed.

Overseas presumptive treatment

Given that the cost of presumptive treatment in Canada could be a concern for the IFHP, and savings may go unnoticed, it is worth discussing another approach: presumptive treatment of refugees before they come to Canada. The United States implemented pre-departure treatment for strongyloides in 1997, following a CDC recommendation, and added schistosomiasis treatment for refugees from sub-Saharan Africa in 2005.(84)

This approach benefits from the availability of low-cost generic drugs in developing countries. For example, in 1995 the World Health Organization reported the retail cost of 600

mg of praziquantel ranged from 0.57 to 2.11 US dollars in Africa and the Middle East.(85) In Canada, where Bayer is the only manufacturer, the cost is approximately 10 times higher.

In part because of this lower drug costs, savings relative to treatment in Canada are likely. For individuals coming to Canada as refugees, for example after referral by the UN High Commission for Refugees, the IFHP could use existing processes to cover pre-departure treatment with locally available generics. In 2017, the program started covering pre-departure treatment for refugees affected by local disease outbreaks, so the incremental cost of adding presumptive treatment with praziquantel would be low. Immigrant Medical Examinations are provided by doctors in the departure country who register with the IFHP.(82, 86) These physicians bill their patients for these services, so additional physician time spent with the patient would not be a cost borne by IFHP.(87) Existing administrative processes around coverage for other treatments could likely incorporate coverage of praziquantel with minimal additional demand on resources. Nor should the capacity to administer praziquantel be a concern. The doctors registered to examine refugees destined for Canada are often the same doctors who already provide presumptive treatment for refugees headed to the United States, through the International Organization for Migration.(84, 86) However, there is a practical limit to the savings that could be realized through overseas presumptive treatment: individuals applying for refugee status from within Canada would still need to be seen by a Canadian doctor and purchase praziquantel at a domestic Canadian price.

Since Canada only began offering overseas treatment to refugees in 2017, and because the CCIRH does not have the same level of influence in Canada as the CDC does in the United States, it is understandable that Canada does not yet offer overseas presumptive treatment for

schistosomiasis and strongyloides to peole who have declared themselves as refugees. But it would appear there is a case to be made for following the American example, because it may reduce the cost of delivering the service that offers patients the greatest benefit.

Overseas presumptive treatment may also provide the best method to offer presumptive treatment equitably. Recent immigrants to Canada are less likely than other Canadians to be attached to a family physician.(88) Some physicians describe the complexity of managing immigrants' health needs as a barrier to taking them on as patients.(89) There is a risk that even if presumptive treatment were to become the recommended standard of practice in Canada, it would not be offered to refugees (and other immigrants) who were not attached to a physician. Providing the treatment prior to departure could ensure better coverage.

Ideally the economic evaluation in chapter 2 would have included overseas presumptive treatment as an alternative. There would be value in performing a new evaluation that includes full costing and estimation of benefits for overseas presumptive treatment for refugees coming to Canada.

This is also a limitation of the CCIRH guideline, which did not consider domestic or overseas presumptive treatment as options.(22) As the analysis in chapter 2 shows, the screening and treatment approach the CCIRH recommended is not cost-effective compared to presumptive treatment. Our analysis also points to a second limitation of the CCIRH guideline: its recommendation to screen refugees from Africa only. (22) The CCIRH guideline does refer to the WHO's finding that 85% of the global burden of illness from schistosomiasis occurs in

Africa(1), as does chapter 1 of this volume. However, it is argued in the first section of this chapter that the risk of infection for refugees from Brazil, Venezuela, China, Laos, Cambodia, the Philippines, and Indonesia is likely high enough to justify screening or presumptive treatment. By the same logic, the CDC's recommendation to presumptively treat US-bound refugees from sub-Saharan Africa (84) should have included other countries; but the CDC did not conduct an economic evaluation for schistosomiasis treatment. These examples demonstrate the value of a full economic evaluation that assesses every option.

For sake of brevity, the study presented in chapter 2 did not consider overseas presumptive treatment as an option, the approach to patient selection, the equity considerations or the potential implementation issues described above. This chapter has attempted to expand on them to provide context for the finding of cost-effectiveness.

References

1 WHO. Schistosomiasis Fact Sheet 2017 [updated January 2017. Available from: http://www.who.int/mediacentre/factsheets/fs115/en/.

2 Davis A. Schistosomiasis. In: Cook GC, Zumla AI, editors. Manson's Tropical Diseases: Elsevier; 2009.

3 Gray DJ, Ross AG, Li YS, McManus DP. Diagnosis and management of schistosomiasis. BMJ (Clinical research ed). 2011;342:d2651.

4 Gryseels B. Schistosomiasis. Infectious Disease Clinics of North America. 2012;26(2):383-97.

5 Haque AK. The Trematodes. In: Barrios R, Haque AK, editors. Parasitic Disease of the Lungs. Berlin: Springer; 2013.

6 King CH. Schistosomiasis. In: Guerrant RL, Walker DH, Weller PF, editors. Tropical Infectious Diseases. Toronto: Elsevier; 2011.

7 Ross AGP, Bartley PB, Sleigh AC, Olds GR, Li Y, Williams GM, et al. Schistosomiasis. New England Journal of Medicine. 2002;346(16):1212-20.

8 Strickland GT. Gastrointestinal manifestations of schistosomiasis. Gut. 1994;35(10):1334-7.

9 Rozendaal JA. Freshwater Snails. Vector control: methods for use by individuals and communities. London: WHO; 1997. p. 337-56.

10 Basch PF, Grodhaus G, Diconza JJ. Introduced Schistosomiasis: Evaluation as a Public Health Hazard. Western Journal of Medicine. 1975;122(2):127-9.

11 Boggild AKAK. Prospective analysis of parasitic infections in Canadian travelers and immigrants. Journal of travel medicine.13(3):138-44.

12 Fontaine JJ. [Imported parasitic diseases: apropos of 4 cases of schistosomiasis]. L'union medicale du Canada.100(5):930-5.

13 Libman MD, MacLean JD, Gyorkos TW. Screening for schistosomiasis, filariasis, and strongyloidiasis among expatriates returning from the tropics. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America. 1993;17(3):353-9.

14 Sekla L, Fast M, Drulak M, Nowicki B. A pilot survey of endemic and imported parasitic infections in Manitoba. Canadian journal of public health = Revue canadienne de sante publique. 1978;69(6):475-80.

15 Costiniuk CT, Cooper CL, Doucette S, Kovacs CM. Parasitic disease screening among HIV patients from endemic countries in a Toronto clinic. The Canadian Journal of Infectious Diseases & Medical Microbiology. 2012;23(1):23-7.

16 Harries AD, Fryatt R, Walker J, Chiodini PL, Bryceson AD. Schistosomiasis in expatriates returning to Britain from the tropics: a controlled study. Lancet (London, England). 1986;1(8472):86-8.

17 Acute schistosomiasis in travellers returning from Africa. Weekly epidemiological record.65(25):194-5.

18 Whitty CJ, Mabey DC, Armstrong M, Wright SG, Chiodini PL. Presentation and outcome of 1107 cases of schistosomiasis from Africa diagnosed in a non-endemic country. Transactions of the Royal Society of Tropical Medicine and Hygiene. 2000;94(5):531-4.

19 Drew LP, Brian GB, Michelle W, Flagg EW, Ortega L, Wilson M, et al. High Prevalence and Presumptive Treatment of Schistosomiasis and Strongyloidiasis among African Refugees. Clinical Infectious Diseases. 2007;45(10):1310-5.

20 Cronin AA, Shrestha D, Cornier N, Abdalla F, Ezard N, Aramburu C. A review of water and sanitation provision in refugee camps in association with selected health and nutrition indicators – the need for integrated service provision. Journal of Water and Health. 2008;6(1):1-13.

21 UNHCR. Refugee Resettlement: An International Handbook to Guide Reception and Integration [Internet]2002. Available from: http://www.unhcr.org/protection/resettlement/4a2cfe336/refugee-resettlement-international-handbook-guide-reception-integration.html.

22 Pottie K, Greenaway C, Feightner J, Welch V, Swinkels H, Rashid M, et al. Evidence-based clinical guidelines for immigrants and refugees. Canadian Medical Association Journal. 2011;183(12):E824-E925.

23 Australasian Society for Infectious Diseases. Recommendations for comprehensive post-arrival health assessment for poeple from refugee-like backgrounds [Internet]. 2016 [cited 2018 July 24]. Available from: https://www.asid.net.au/documents/item/1225.

24 Intestinal Parasite Guidelines for Domestic Medical Examination for Newly Arrived Refugees [Internet]. Centers for Disease Control and Prevention. 2013. Available from: https://www.cdc.gov/immigrantrefugeehealth/pdf/intestinal-parasites-domestic.pdf.

25 Khan K. question about CCIRH guideline uptake. In: Webb J, editor. 2017.

26 Drummond MF, Sculpher MJ, Torrance GW, O'Brien BJ, Stoddart GL. Methods for the Economic Evaluation of Health Care Programmes, 3rd ed. Oxford: Oxford University Press; 2005.

27 Murray CJ, Lopez AD, Jamison DT. The global burden of disease in 1990: summary results, sensitivity analysis and future directions. Bull World Health Organ. 1994;72(3):495-509.

28 Winsberg GR, Moriearty P, Yogore M, Lewert R. Schistosomiasis In Chicago: A Study Of The Westown Puerto Rican Population. American Journal of Epidemiology. 1974;100(4):324-32.

29 Wiest PM, Wu G, Zhong S, McGarvey ST, Tan E, Yuan J, et al. Schistosomiasis japonica on Jishan Island, Jiangxi Province, People's Republic of China: persistence of hepatic fibrosis after reduction of the prevalence of infection with age. Transactions of the Royal Society of Tropical Medicine and Hygiene. 1993;87(3):290-4.

30 Strauss E. Hepatosplenic schistosomiasis: a model for the study of portal hypertension. Annals of hepatology. 2002;1(1):6-11.

31 Smith JH, Kamel IA, Elwi A, von Lichtenberg F. A Quantitative Post Mortem Analysis of Urinary Schistosomiasis in Egypt. The American journal of tropical medicine and hygiene. 1974;23(6):1054-71.

32 Saad AM, Homeida M, Eltom I, Nash T, Bennett JL, Hassan MA. Oesophageal varices in a region of the Sudan endemic for Schistosoma mansoni. The British journal of surgery. 1991;78(10):1252-3.

33 Mudawi H, Ali Y, Tahir ME. Prevalence of gastric varices and portal hypertensive gastropathy in patients with Symmers periportal fibrosis. Annals of Saudi Medicine. 2008;28:42.

34 Morris W, Knauer CM. Cardiopulmonary manifestations of schistosomiasis. Semin Respir Infect. 1997;12(2):159-70.

35 King CH, Keating CE, Muruka JF, Ouma JH, Houser H, Siongok TK, et al. Urinary tract morbidity in schistosomiasis haematobia: associations with age and intensity of infection in an endemic area of Coast Province, Kenya. The American journal of tropical medicine and hygiene. 1988;39(4):361-8.

36 Gelfand M, Ross MD, Blair DM, Weber MC. Distribution and extent of schistosomiasis in female pelvic organs, with special reference to the genital tract, as determined at autopsy. The American journal of tropical medicine and hygiene. 1971;20(6):846-9.

37 El-Khoby T, Galal N, Fenwick A, Barakat R, El-Hawey A, Nooman Z, et al. The epidemiology of schistosomiasis in Egypt: summary findings in nine governorates. The American journal of tropical medicine and hygiene. 2000;62(2_suppl):88-99.

38 de Cleva R, Herman P, Pugliese V, Zilberstein B, Saad WA, Rodrigues JJG, et al. Prevalence of pulmonary hypertension in patients with hepatosplenic Mansonic schistosomiasis--prospective study. Hepatogastroenterology. 2003;50(54):2028-30.

39 Cheever AW, Andrade ZA. Pathological lesions associated with schistosoma mansoni infection in man. Transactions of the Royal Society of Tropical Medicine and Hygiene. 1967;61(5):626-39.

40 Andrade ZA. The situation of hepatosplenic schistosomiasis in Brazil today. Memorias do Instituto Oswaldo Cruz. 1998;93:313-6.

41 Posey DL, Blackburn BG, Weinberg M, Flagg EW, Ortega L, Wilson M, et al. High Prevalence and Presumptive Treatment of Schistosomiasis and Strongyloidiasis among African Refugees. Clinical Infectious Diseases. 2007;45(10):1310-5.

42 Miller JM, Boyd HA, Ostrowski SR, Cookson ST, Parise ME, Gonzaga PS, et al. Malaria, intestinal parasites, and schistosomiasis among Barawan Somali refugees resettling to the United States: a strategy to reduce morbidity and decrease the risk of imported infections. The American journal of tropical medicine and hygiene. 2000;62(1):115-21.

43 Warren KS, Mahmoud AAF, Cummings P, Murphy DJ, Houser HB. Schistosomiasis Mansoni in Yemeni in California: Duration of Infection, Presence of Disease, Therapeutic Management*. The American journal of tropical medicine and hygiene. 1974;23(5):902-9.

44 Imperato PJP. A study of patient populations in New York City tropical disease clinics. Acta tropica. 1974;31(2):97-107.

45 Imperato PJP. Parasitic infections in New York City. Incidence and epidemiology. New York state journal of medicine. 1977;77(1):50-6.

46 Woodson RGR. Schistosomiasis in Oklahoma. Journal - Oklahoma State Medical Association.72(8):293-7.

47 Muennig P, Pallin D, Sell RL, Chan MS. The cost effectiveness of strategies for the treatment of intestinal parasites in immigrants. The New England journal of medicine. 1999;340(10):773-9.

48 Chang AH, Perry S, Du JNT, Agunbiade A, Polesky A, Parsonnet J. Decreasing Intestinal Parasites in Recent Northern California Refugees. The American journal of tropical medicine and hygiene. 2013;88(1):191-7.

49 Carabin H, Guyatt H, Engels D. A comparative analysis of the cost-effectiveness of treatment based on parasitological and symptomatic screening for Schistosoma mansoni in Burundi. Tropical medicine & international health : TM & IH. 2000;5(3):192-202.

50 Kirigia JM. Economic evaluation in schistosomiasis: using the Delphi technique to assess effectiveness. Acta tropica. 1997;64(3-4):175-90.

51 Wright WH. A consideration of the economic impact of schistosomiasis. Bull World Health Organ. 1972;47(5):559-65.

52 Muennig P, Pallin D, Sell RL, Chan M-S. The Cost Effectiveness of Strategies for the Treatment of Intestinal Parasites in Immigrants. New England Journal of Medicine. 1999;340(10):773-9.

53 Maskery B, Coleman MS, Weinberg M, Zhou W, Rotz L, Klosovsky A, et al. Economic Analysis of the Impact of Overseas and Domestic Treatment and Screening Options for Intestinal Helminth Infection among US-Bound Refugees from Asia. PLoS neglected tropical diseases. 2016;10(8):e0004910.

54 Anderson JP, Moser RJ. Parasite screening and treatment among Indochinese refugees. Cost-benefit/utility and the General Health Policy Model. Jama. 1985;253(15):2229-35.

55 NRCP. Immunodiagnostic Services: J.D. Maclean Centre for Tropical Diseases; 2018 [Available from: https://www.mcgill.ca/tropmed/services/national-reference-centre-parasitology/immunodiagnostic-service].

56 Danso-Appiah A, Olliaro PL, Donegan S, Sinclair D, Utzinger J. Drugs for treating Schistosoma mansoni infection. Cochrane Database of Systematic Reviews. 2013(2).

57 Vermund SH. Survival of Schistosoma mansoni in the human host: estimates from a community-based prospective study in Puerto Rico. The American journal of tropical medicine and hygiene.32(5):1040-8.

58 Goddard MJ, Jordan P. On the longevity of Schistosoma mansoni in man on St. Lucia, West Indies. Transactions of the Royal Society of Tropical Medicine and Hygiene. 1980;74(2):185-91.

59 Harris ARC, Russell RJ, Charters AD. A review of schistosomiasis in immigrants in Western Australia, demonstrating the unusual longevity of Schistosoma mansoni. Transactions of the Royal Society of Tropical Medicine and Hygiene. 1984;78(3):385-8.

60 Fatureto MC, Correia D, Silva MBdO, Barra MFC, Silva AVd, Tarquinio DC, et al. Nódulo pulmonar esquistossomótico simulando neoplasia: relato de caso. Revista da Sociedade Brasileira de Medicina Tropical. 2003;36(6).

61 Lambertucci JR, Moreira RF, Barbosa AJA. Solitary pulmonary nodule caused by Schistosoma mansoni in a patient with medullary thyroid carcinoma. Revista da Sociedade Brasileira de Medicina Tropical. 2005;38(6).

62 de Górgolas M, Casado V, Renedo G, Alen JF, Guerrero MLF. Nodular Lung Schistosomiais Lesions after Chemotherapy for Dysgerminoma. The American journal of tropical medicine and hygiene. 2009;81(3):424-7.

63 Sullivan, P.W., W.F. Lawrence, and V. Ghushchyan, A National Catalog of Preference-Based Scores for Chronic Conditions in the United States. Medical Care, 2005. 43(7): p. 736-749.

64 Building Alberta: Health a priority in Budget 2013 [Internet]. Government of Alberta; 2013 [cited 2017 July 10]. Available from: https://www.alberta.ca/release.cfm?xID=3377946A8CD70-C069-7894-1D9786D5EBBD7C8E.

65 Briggs A, Claxton K, Sculpher M. Decision Modelling for Health Economic Evaluation. Toronto: Oxford; 2006.

66 Hoyle MW, Henley W. Improved curve fits to summary survival data: application to economic evaluation of health technologies. BMC medical research methodology. 2011;11:139.

67 Lamour P, Bouree P, Hennequin C, Lombrail P, Squinazi F, Roussel C, et al. [Blind treatment or treatment oriented to intestinal parasitoses in a Parisian health center for refugees]. Sante (Montrouge, France). 1994;4(1):21-6.

68 Centre for Refugee Studies. Global Refugee Crisis [Internet]. York University; 2018 [cited 2018 July 24]. Available from: http://crs.info.yorku.ca/global-refugee-crisis.

69 Davis A, Biles JE, Ulrich AM. Initial experiences with praziquantel in the treatment of human infections due to Schistosoma haematobium. Bulletin of the World Health Organization. 1979;57(5):773-9.

70 Life Tables, Canada, Provinces and Territories (2010-2012, no. 6): Statistics Canada; 2017 [Available from: http://www.statcan.gc.ca/access_acces/alternative_alternatif.action?loc=/pub/84-537-x/2016006/2016006-eng.xlsx.

71 Gaitatzis A, Johnson AL, Chadwick DW, Shorvon SD, Sander JW. Life expectancy in people with newly diagnosed epilepsy. Brain : a journal of neurology. 2004;127(Pt 11):2427-32.

72 CIHI. Patient Cost Estimator [Available from: https://www.cihi.ca/en/patient-cost-estimator.

73 Interim Federal Health Program: Summary of Coverage [Internet]. Government of Canada; 2018 [cited 2018 July 24]. Available from: https://www.canada.ca/en/immigration-refugees-citizenship/services/refugees/help-within-canada/health-care/interim-federal-health-program/coverage-summary.html.

74 Life tables, Canada, provinces and territories. [Internet]. 2015. Available from: https://www150.statcan.gc.ca/n1/pub/84-537-x/2018001/xls/2013-2015_Tbl-eng.xlsx.

75 Collins JA, Burrows EA, Willan A. Infertile couples and their treatment in Canadian academic infertility clinics. Royal Commission on New Reproductive Technologies, Treatment of Infertility: Current Practices and Psychological Implications. Ottawa: Ministry of Supply and Services Canada; 1993. p. 243.

76 CADTH Guideline Working Group. Guidelines for the Economic Evaluation of Health Technologies: Canada. CADTH; 2017 March.

77 Doumenge J, Mott K, Cheung C, Villenave D, Chapuis O, Perrin M, et al. Global Schistosomias Atlas [Internet]: World Health Organization; 1987 [cited 2018 July 1]. Available from: http://www.who.int/schistosomiasis/epidemiology/global_atlas/en/.

78 Status of schistosomiasis endemic countries [Internet]. World Health Organization; 2016 [cited 2018 July 1]. Available from: http://apps.who.int/neglected_diseases/ntddata/sch/sch.html.

79 World Health Organization. Schistosomiasis: population requiring preventive chemotherapy and number of people treated in 2010. Weekly epidemiological record. 2012;4(87):8.

80 Refugee Protection Claims Statistics [Internet]. Immigration and Refugee Board of Canada; 2018 [cited 2018 June 28]. Available from: http://www.irb-cisr.gc.ca/Eng/RefClaDem/stats/Pages/index.aspx.

81 Budgetary Decisions by Allotment [Internet]. Government of Canada; 2017 [cited 2018 June 28]. Available from: https://www.tpsgc-pwgsc.gc.ca/recgen/cpc-pac/2017/vol2/ircc/dba-bda-eng.html

82 Liberal government fully restores refugee health care program [Internet]. CBC News; 2016 [cited 2018 June 30]. Available from: https://www.cbc.ca/news/politics/mcallum-philpott-interim-federal-health-program-refugees-1.3453397.

83 National Reference Centre for Parasitology [Internet]. McGill University; [cited 2018 June 28]. Available from: https://www.mcgill.ca/tropmed/services/national-reference-centre-parasitology.

84 Centers for Disease Control and Prevention DoGMaQ. Guidelines for Overseas Presumptive Treatment of Strongyloidiasis, Schistosomiasis, and Soil-Transmitted Helminth Infections 2013 [cited 2018 June 28]. Available from: https://www.cdc.gov/immigrantrefugeehealth/guidelines/overseas/intestinal-parasites-overseas.html.

85 Govindaraj R, Reich MR, Dumbaughm K. The price of praziquantel. 1995. In: International Strategies for Tropical Disease Treatments - Experiences with Praziquantel [Internet]. Available from: http://apps.who.int/medicinedocs/en/d/Jwhozip48e/11.html.

86 Get medical services before you leave for Canada [Internet]. Government of Canada; 2017 [cited 2018 June 28]. Available from: https://www.canada.ca/en/immigration-refugees-citizenship/services/refugees/help-outside-canada/health-care.html.

87 Panel Member's Handbook [Internet]. Government of Canada; 2013 [cited 2019 January 3]. Available from https://www.canada.ca/en/immigration-refugees-citizenship/corporate/publications-manuals/panel-members-handbook-2013.html.

88 Hay C, Pacey M, Bains N, Ardal S. Understanding the Unattached Population in Ontario: Evidence from the Primary Care Access Survey (PCAS). Healthcare Policy. 2010;6(2):33-47.

89 Lorena M, Maureen M, J. GK, Ricardo B, Kevin P. Rejecting and accepting international migrant patients into primary care practices: a mixed method study. International Journal of Migration, Health and Social Care. 2015;11(2):108-29.

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' adherence to creening 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. 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.[2] 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.

Lifetime 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.[3-5] Others were obtained from clinicians' descriptions of what proportion of individuals infected with schistosomiasis go on to develop symptoms.[6-9] The probability of pyelonephritis progressing to bacteremia was obtained from a study of catheter-associated urinary tract infections.[10] 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. These probabilities are summarized in table 1.

Table 1) Model parameters

Parameter	**Value**	**Range**	**Reference**
Mean age of patients (yrs)	35.9	-	Unpublished data
Age of symptom onset (yrs)	55	36 - 84	[1]
probability of patient being female	0.487	-	Unpublished data
probability of patient being infected	0.232	0.181 - 0.293	Unpublished data
probability of test being (+) given presence of infection	0.99	-	[11]
probability of test being (-) given absence of infection	0.90	-	[11]
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	[1, 12]
probability of hepatosplenic (vs. urinary) involvement, given infection	0.45	-	Unpublished data
probability of urinary obstruction, given infection	0.287	0 - 0.431	[3]
probability of hydronephrosis, given infection	0.228	0 – 0.342	[3]
probability of pyelonephritis, given obstruction	0.197	0 - 0.295	[3]
probability of bacteremia, given pyelonephritis	0.143	0 – 0.341	[10]
probability of genital disease, given infection in female	0.333	0 – 0.500	[5]
probability of carcinoma, given infection	0.027	0 - 0.041	[3]
probability of intestinal disease, given infection	0.133	0 - 0.200	[6]
probability of portal fibrosis, given infection	0.139	0 - 0.209	[4]
probability of ascites, given fibrosis	0.070	0.010 - 0.100	[9]
probability of hematemesis, given fibrosis	0.027	0 - 0.040	[8]
probability of death, given hematemesis	0.153	0 - 0.230	[7]
probability of pulmonary hypertension, given fibrosis	0.186	0 - 0.230	[6]
probability of cor pulmonale, given fibrosis	0.050	0 - 0.075	[6]

probability of glomerulonephritis, given fibrosis	0.067	0 - 0.100	[6]
probability of CNS involvement, given infection	0.001	0 - 0.002	[4]
Survival if no schistosomiasis complications (yrs)	28.9	-	[13]
Mean survival for glomerulonephritis (yrs)	17.3	-	[14]
Mean survival for pulmonary hypertension (yrs)	9.4	-	[15]
Mean survival for bladder cancer (yrs)	5.3	-	[16]
Mean survival for cor pulmonale (yrs)	7.0	-	[17]
Mean survival for portal hypertension (yrs)	27.8	-	[18]
Years of treatment for infertility	4.1	-	[19]
Utility discount rate (%)	1.5	-	[20]
Cost discount rate (%)	1.5	-	[20]
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.

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. [11] 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.[19]

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 2.

Table 2) 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	[21]
Ascites	Family physician, internist	Spironolactone 100 mg po daily	CBC, electrolytes	[22, 23]
Cor pulmonale	Family physician, cardiologist	Furosemide 60 mg po daily	(patient will already have tests ordered for pulmonary hypertension)	[24]
Variceal hemorrhage	Family physician, gastroenterologist	Propranolol 200 mg po daily	CBC, electrolytes, esophagogastroscopy	[25, 26]
Pulmonary hypertension	Family physician, respirologist	Diltiazem 480 mg po daily	CBC, electrolytes	[27]

*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.[28] 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 3.

Table 3) 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 2 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 4) Various costs used in the model

Item	**Cost**	**Reference**
Family physician visit	$51.37	[29]
Consult – urologist	$99.18	[29]
Consult – internist	$204.39	[29]
Consult – cardiologist	$127.21	[29]
Consult – nephrologist	$155.83	[29]
Consult – gastroenterologist	$119.96	[29]
Consult – respirologist	$124.22	[29]
Spironolactone 100 mg per	$0.53	[30]
Propanolol 200 mg per day	$0.26	[30]
Furosemide 60 mg per day	$0.11	[30]
Diltiazem 480 mg per day	$0.77	[30]
Complete Blood Count	$8.27	[31]
Electrolytes	$7.76	[31]
Creatinine	$2.59	[31]
Albumin	$1.55	[31]
Bilirubin	$2.59	[31]
CT Pelvis	$247.60	[32]
Esophagogastroscopy	$572.27	[32]

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.[33] 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.[14-18] Using Stata 15 software, different types of hazard functions (Gompertz, Exponential, Lognormal, Loglogistic and Weibull) were fit to survival study data.[34] 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.[33, 35] 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*. [36] 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.[37] These are described in table 5.

Table 5) Disease states and associated utility decrements

Schistosomiasis complication	**Analogous health state**	**Disutility**	**Standard error**	**Reference**
CNS involvement	Acute cerebrovascular disease	0.0483	0.0009	[36]
Cor pulmonale	CHF, nonhypertensive	0.0546	0.0010	[36]
Malabsorption	Other gastrointestinal disorders	0.0315	0.0005	[36]
Variceal hemorrhage -	Gastric ulcer	0.0269	0.0002	[38]
Glomerulonephritis	Other diseases of the kidney	0.0544	0.0011	[36]
Ascites	Other liver diseases	0.0184	0.0013	[36]
Pulmonary hypertension	Other lung disease	0.0428	0.0002	[38]
Infertility	Infertility	0.070	-	[37]
Bladder carcinoma	Unspecified neoplasm	0.0174	0.0001	[38]
Pyelonephritis	Other diseases of the kidney	0.0544	0.0011	[36]
Genital schistosomiasis	Other female genital disorders	0.015	0.0007	[36]

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

References

1. Whitty, C.J., et al., *Presentation and outcome of 1107 cases of schistosomiasis from Africa diagnosed in a non-endemic country.* Trans R Soc Trop Med Hyg, 2000. **94**(5): p. 531-4.
2. WHO. *Schistosomiasis Fact Sheet*. 2017 January 2017 [cited 2017 July 3]; Available from: http://www.who.int/mediacentre/factsheets/fs115/en/.
3. Smith, J.H., et al., *A Quantitative Post Mortem Analysis of Urinary Schistosomiasis in Egypt.* The American Journal of Tropical Medicine and Hygiene, 1974. **23**(6): p. 1054-1071.
4. Cheever, A.W. and Z.A. Andrade, *Pathological lesions associated with schistosoma mansoni infection in man.* Transactions of the Royal Society of Tropical Medicine and Hygiene, 1967. **61**(5): p. 626-639.
5. Gelfand, M., et al., *Distribution and extent of schistosomiasis in female pelvic organs, with special reference to the genital tract, as determined at autopsy.* Am J Trop Med Hyg, 1971. **20**(6): p. 846-9.
6. Prata, A., *Infection with S. mansoni*, in *Schistosomiasis: Epidemiology, Treatment and Control*, P. Jordan and G. Webbe, Editors. 1982, William Heinemann Medical Books: London. p. 105-127.
7. Reboucas, G., *Clinical aspects of hepatosplenic schistosomiasis: a contrast with cirrhosis.* Yale J Biol Med, 1975. **48**(5): p. 369-76.
8. Saad, A.M., et al., *Oesophageal varices in a region of the Sudan endemic for Schistosoma mansoni.* Br J Surg, 1991. **78**(10): p. 1252-3.
9. Andrade, Z.A., *The situation of hepatosplenic schistosomiasis in Brazil today.* Memórias do Instituto Oswaldo Cruz, 1998. **93**: p. 313-316.
10. Stamm, W.E., *Catheter-associated urinary tract infections: epidemiology, pathogenesis, and prevention.* Am J Med, 1991. **91**(3b): p. 65s-71s.
11. NRCP. *Immunodiagnostic Services*. 2018 [cited 2018 May 22]; Available from: www.mcgill.ca/tropmed/services/national-reference-centre-parasitoloty/immunodiagnostic-service.
12. Danso-Appiah, A., et al., *Drugs for treating Schistosoma mansoni infection.* Cochrane Database of Systematic Reviews, 2013(2).
13. Statistics Canada, *Life tables, Canada, provinces and territories.*, in *Catalogue no. 84-537-X*. 2015: Ottawa.
14. Heaf, J., H. Løkkegaard, and S. Larsen, *The epidemiology and prognosis of glomerulonephritis in Denmark 1985–1997.* Nephrology Dialysis Transplantation, 1999. **14**(8): p. 1889-1897.
15. Oswald-Mammosser, M., et al., *Prognostic Factors in COPD Patients Receiving Long-term Oxygen Therapy: Importance of Pulmonary Artery Pressure.* Chest, 1995. **107**(5): p. 1193-1198.
16. Ehdaie, B., et al., *Comparative Outcomes of Pure Squamous Cell Carcinoma and Urothelial Carcinoma With Squamous Differentiation in Patients Treated With Radical Cystectomy.* The Journal of urology, 2012. **187**(1): p. 74-79.
17. Opitz, C.F., et al., *Pre-Capillary, Combined, and Post-Capillary Pulmonary Hypertension: A Pathophysiological Continuum.* Journal of the American College of Cardiology, 2016. **68**(4): p. 368-378.
18. Siramolpiwat, S., et al., *Idiopathic portal hypertension: natural history and long-term outcome.* Hepatology, 2014. **59**(6): p. 2276-85.
19. Collins, J.A., E.A. Burrows, and A. Willan, *Infertile couples and their treatment in Canadian academic infertility clinics*, in *Royal Commission on New Reproductive Technologies, Treatment of Infertility: Current Practices and Psychological Implications*. 1993, Ministry of Supply and Services Canada: Ottawa. p. 243.

20. CADTH Guideline Working Group, *Guidelines for the Economic Evaluation of Health Technologies: Canada*. 2017, CADTH.
21. Kassouf, W., et al., *Recommendations for the improvement of bladder cancer quality of care in Canada: A consensus document reviewed and endorsed by Bladder Cancer Canada (BCC), Canadian Urologic Oncology Group (CUOG), and Canadian Urological Association (CUA), December 2015.* Can Urol Assoc J, 2016. **10**(1-2): p. E46-80.
22. Runyon, B.A., *Management of Adult Patients with Ascites due to Cirrhosis: Update 2012*, in *Practice Guideline*. 2012, AASLD.
23. *Health-Lifestyles News Advisory as of 5 p.m. ET Thursday, Feb. 5*, in *The Canadian Press*. 2015: Toronto.
24. Howlett, J.G., et al., *Canadian Cardiovascular Society Consensus Conference guidelines on heart failure, update 2009: diagnosis and management of right-sided heart failure, myocarditis, device therapy and recent important clinical trials.* Can J Cardiol, 2009. **25**(2): p. 85-105.
25. Garcia-Tsao, G., et al., *Portal hypertensive bleeding in cirrhosis: Risk stratification, diagnosis, and management: 2016 practice guidance by the American Association for the study of liver diseases.* Hepatology, 2017. **65**(1): p. 310-335.
26. European Association for the Study of the Liver, *EASL Clinical Practice Guidelines: Vascular diseases of the liver.* J Hepatol, 2016. **64**(1): p. 179-202.
27. Provencher, S. and J.T. Granton, *Current treatment approaches to pulmonary arterial hypertension.* Can J Cardiol, 2015. **31**(4): p. 460-77.
28. CIHI. *Patient Cost Estimator*. Available from: https://www.cihi.ca/en/patient-cost-estimator.
29. *Alberta Health Care Insurance Plan: Schedule of Medical Benefits*. [Internet] 2018; Available from: https://open.alberta.ca/publications/somb-2017-04-01.
30. *Alberta Drug Benefit List*. 2018; Available from: https://www.ab.bluecross.ca/dbl/publications.html#dbl.
31. *Schedule of Benefits for Laboratory Services*. [Internet] 2017; Available from: http://www.health.gov.on.ca/en/pro/programs/ohip/sob/lab/lab_mn.pdf.
32. Coyle, K., et al., *Cost effectiveness of the addition of a comprehensive CT scan to the abdomen and pelvis for the detection of cancer after unprovoked venous thromboembolism.* Thrombosis Research, 2017. **151**: p. 67-71.
33. *Life Tables, Canada, Provinces and Territories (2010-2012, no. 6)*. 2017 [cited 2017 July 8]; Available from: http://www.statcan.gc.ca/access_acces/alternative_alternatif.action?loc=/pub/84-537-x/2016006/2016006-eng.xlsx.
34. StataCorp, *Stata Statistical Software*. 2017, StataCorp LLC: College Station, TX.
35. Gaitatzis, A., et al., *Life expectancy in people with newly diagnosed epilepsy.* Brain, 2004. **127**(Pt 11): p. 2427-32.
36. Sullivan, P.W., W.F. Lawrence, and V. Ghushchyan, *A National Catalog of Preference-Based Scores for Chronic Conditions in the United States.* Medical Care, 2005. **43**(7): p. 736-749.
37. Scotland, G., et al., *Minimising twins in in vitro fertilisation: a modelling study assessing the costs, consequences and cost–utility of elective single versus double embryo transfer over a 20-year time horizon.* BJOG: An International Journal of Obstetrics & Gynaecology, 2011. **118**(9): p. 1073-1083.
38. Sullivan, P.W. and V. Ghushchyan, *Preference-Based EQ-5D Index Scores for Chronic Conditions in the United States.* Medical Decision Making, 2006. **26**(4): p. 410-420.

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.

References

1. Whitty, C.J., et al., *Presentation and outcome of 1107 cases of schistosomiasis from Africa diagnosed in a non-endemic country.* Trans R Soc Trop Med Hyg, 2000. **94**(5): p. 531-4.
2. Statistics Canada, *Census Profile. 2016 Census*, in *Statistics Canada Catalogue no. 98-316-X2016001.* 2017: Ottawa.
3. *Facts about immigrants*. [Internet] 2007; Available from: https://www.calgary.ca/CSPS/CNS/Documents/Social-research-policy-and-resources/facts-immigrants.pdf?noredirect=1.

Appendix 3

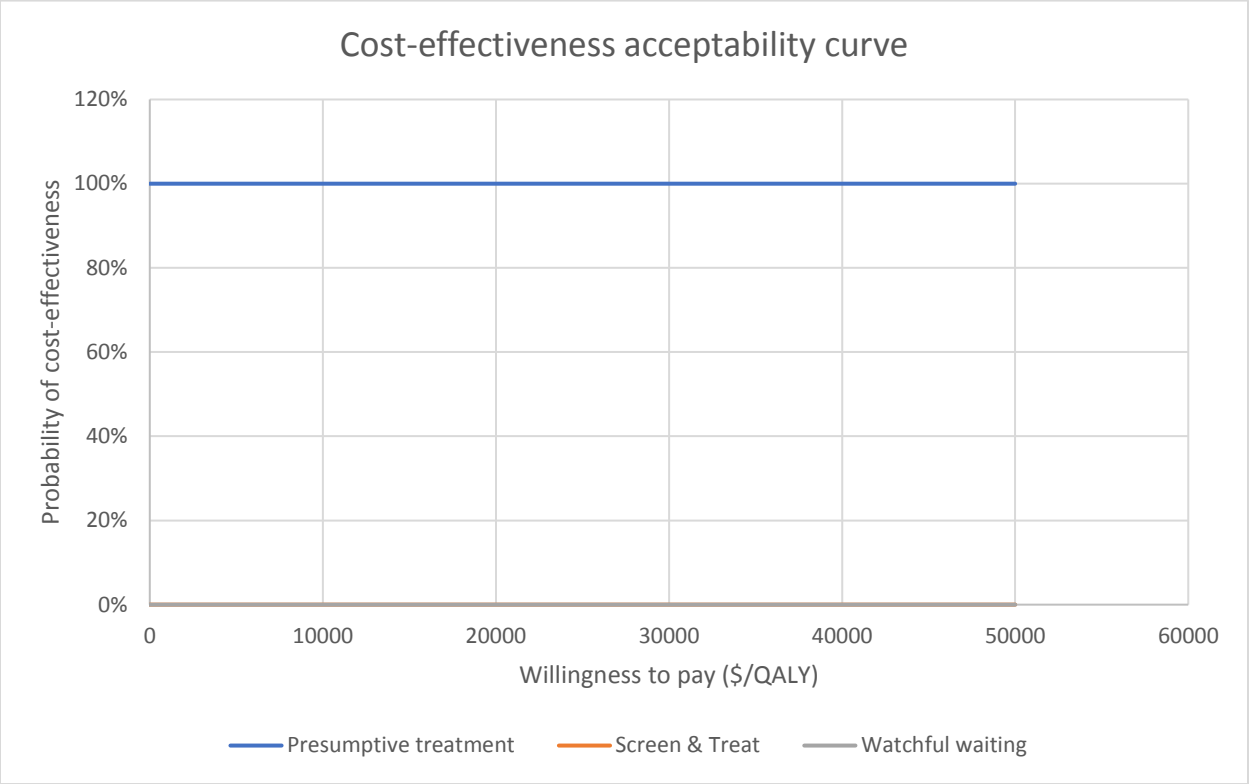
One-way sensitivity analysis and scenario analysis

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 %

Appendix 6

CHEERS checklist

CHEERS checklist—Items to include when reporting economic evaluations of health interventions

Section/item	Item No	Recommendation	Reported on page No/ line No
Title and abstract			
Title	1	Identify the study as an economic evaluation or use more specific terms such as "cost-effectiveness analysis", and describe the interventions compared.	Page ii
Abstract	2	Provide a structured summary of objectives, perspective, setting, methods (including study design and inputs), results (including base case and uncertainty analyses), and conclusions.	Page ii
Introduction			
Background and objectives	3	Provide an explicit statement of the broader context for the study.	Page 13
		Present the study question and its relevance for health policy or practice decisions.	Page 14
Methods			
Target population and subgroups	4	Describe characteristics of the base case population and subgroups analysed, including why they were chosen.	Page 14
Setting and location	5	State relevant aspects of the system(s) in which the decision(s) need(s) to be made.	Page 13
Study perspective	6	Describe the perspective of the study and relate this to the costs being evaluated.	Page 20
Comparators	7	Describe the interventions or strategies being compared and state why they were chosen.	Page 16
Time horizon	8	State the time horizon(s) over which costs and consequences are being evaluated and say why appropriate.	Page 21
Discount rate	9	Report the choice of discount rate(s) used for costs and outcomes and say why appropriate.	Page 21
Choice of health outcomes	10	Describe what outcomes were used as the measure(s) of benefit in the evaluation and their relevance for the type of analysis performed.	Page 20
Measurement of	11a	*Single study-based estimates:* Describe fully the	Page 8

Section/item	Item No	Recommendation	Reported on page No/ line No
effectiveness		design features of the single effectiveness study and why the single study was a sufficient source of clinical effectiveness data.	(chapter 1)
	11b	*Synthesis-based estimates:* Describe fully the methods used for identification of included studies and synthesis of clinical effectiveness data.	
Measurement and valuation of preference based outcomes	12	If applicable, describe the population and methods used to elicit preferences for outcomes.	Page 4
Estimating resources and costs	13a	*Single study-based economic evaluation:* Describe approaches used to estimate resource use associated with the alternative interventions. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs.	
	13b	*Model-based economic evaluation:* Describe approaches and data sources used to estimate resource use associated with model health states. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs.	Page 57 (Appendix 1)
Currency, price date, and conversion	14	Report the dates of the estimated resource quantities and unit costs. Describe methods for adjusting estimated unit costs to the year of reported costs if necessary. Describe methods for converting costs into a common currency base and the exchange rate.	Not done
Choice of model	15	Describe and give reasons for the specific type of decision-analytical model used. Providing a figure to show model structure is strongly recommended.	Page 17
Assumptions	16	Describe all structural or other assumptions underpinning the decision-analytical model.	Page 17
Analytical methods	17	Describe all analytical methods supporting the evaluation. This could include methods for dealing with skewed, missing, or censored data; extrapolation methods; methods for pooling data; approaches to validate or make adjustments (such as	Page 20-21

Section/item	Item No	Recommendation	Reported on page No/ line No
		half cycle corrections) to a model; and methods for handling population heterogeneity and uncertainty.	
Results			
Study parameters	18	Report the values, ranges, references, and, if used, probability distributions for all parameters. Report reasons or sources for distributions used to represent uncertainty where appropriate. Providing a table to show the input values is strongly recommended.	Appendix 1
Incremental costs and outcomes	19	For each intervention, report mean values for the main categories of estimated costs and outcomes of interest, as well as mean differences between the comparator groups. If applicable, report incremental cost-effectiveness ratios.	Page 22
Characterising uncertainty	20a	*Single study-based economic evaluation:* Describe the effects of sampling uncertainty for the estimated incremental cost and incremental effectiveness parameters, together with the impact of methodological assumptions (such as discount rate, study perspective).	
	20b	*Model-based economic evaluation:* Describe the effects on the results of uncertainty for all input parameters, and uncertainty related to the structure of the model and assumptions.	Page 23
Characterising heterogeneity	21	If applicable, report differences in costs, outcomes, or cost-effectiveness that can be explained by variations between subgroups of patients with different baseline characteristics or other observed variability in effects that are not reducible by more information.	Not done
Discussion			
Study findings, limitations, generalisability, and current knowledge	22	Summarise key study findings and describe how they support the conclusions reached. Discuss limitations and the generalisability of the findings and how the findings fit with current knowledge.	Page 28
Other			
Source of funding	23	Describe how the study was funded and the role of the funder in the identification, design, conduct, and	Not done in thesis, but

Section/item	Item No	Recommendation	Reported on page No/ line No
		reporting of the analysis. Describe other non-monetary sources of support.	done in paper for submission.
Conflicts of interest	24	Describe any potential for conflict of interest of study contributors in accordance with journal policy. In the absence of a journal policy, we recommend authors comply with International Committee of Medical Journal Editors recommendations.	Not done in thesis, but in paper for submission.

For consistency, the CHEERS statement checklist format is based on the format of the CONSORT statement checklist