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## The cost-effectiveness of ivermectin vs. albendazole in the presumptive treatment of strongyloidiasis in immigrants to the United States

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### SUMMARY

The presumptive treatment of parasitosis among immigrants with albendazole has been shown to save both money and lives, primarily via a reduction in the burden of *Strongyloides stercoralis*. Ivermectin is more effective than albendazole, but is also more expensive. This coupled with confusion surrounding the cost-effectiveness of guiding therapy based on eosinophil counts has led to disparate practices. We used the newly arrived year 2000 immigrant population as a hypothetical cohort in a decision analysis model to examine the cost-effectiveness of various interventions to reduce parasitosis among immigrants. When the prevalence of *S. stercoralis* is greater than 2%, the incremental cost-effectiveness ratios of all presumptive treatment strategies were similar. Ivermectin is associated with an incremental cost-effectiveness ratio of \$1700 per QALY gained for treatment with 12 mg ivermectin relative to 5 days of albendazole when the prevalence is 10%. Any presumptive treatment strategy is cost-effective when compared with most common medical interventions.

### INTRODUCTION

The worldwide burden of intestinal parasitic disease exceeds 3 billion persons [1]. In 2000, approximately 28·4 million foreign-born persons resided in the United States, with most originating from countries where intestinal parasites are endemic [2]. When evaluating new immigrants for parasitic infections, physicians may choose watchful waiting, use eosinophilia as a method to identify high-risk patients, screen for parasitosis using one or more stool examinations, or treat presumptively. Factors to consider when

deciding among these options include the fact that intestinal parasites are common in new immigrant populations, anti-parasitic agents are effective, safe, and well tolerated, and stool examinations for parasites are labour intensive, costly, and highly insensitive at identifying infection [3, 4].

Among intestinal parasites that are common in new immigrant populations, *S. stercoralis* results in the greatest medical costs, morbidity, and loss of life [4]. This parasite is capable of autoinfection, a phenomenon in which the parasite completes its entire life-cycle within the host, thus leading to multiple generations of new organisms and persistent infection for decades [5, 6]. In contrast, most parasites have a more limited lifespan or rarely result in serious illness or death. While the majority of persons infected with

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*S. stercoralis* either remain asymptomatic or develop mild illness, those who subsequently become immunocompromised are at high risk of developing hyperinfection syndrome, a life-threatening disseminated infection with a mortality rate over 50% despite treatment [7].

A prior cost-effectiveness analysis found that presumptive treatment of immigrants with albendazole could save lives and money; basing treatment decisions on stool analysis was more expensive and less effective than presumptive treatment [4]. This analysis included various parasites, and found that both gains in quality-adjusted life and economic benefits hinged on the eradication of *S. stercoralis*, the organism responsible for the hyperinfection syndrome. The analysis did not evaluate the practice of basing clinical decisions on eosinophil counts and did not evaluate alternative presumptive treatment modalities.

Ivermectin, a newer anti-parasitic agent, is more effective against *S. stercoralis* than albendazole and is administered as a single dose, but is narrower in its spectrum of activity and considerably more expensive than albendazole. Therefore, there is uncertainty surrounding the optimal medication for the presumptive treatment of this parasite in immigrants, especially among those at high risk for strongyloidiasis.

We compare the cost-effectiveness of treatment with single-dose ivermectin with two commonly employed regimens of albendazole as well as treatment based on eosinophil counts. Immigrants are often screened for anaemia using a complete blood count (CBC) with differential. Information on a patient's eosinophil count is, therefore, available to clinicians at no cost; thus, screening for eosinophilia is intuitively cost-effective. We, therefore, also report the cost-effectiveness of treating immigrants with known eosinophilia (defined as an absolute eosinophil count >500 or percentage of total leukocytes >5%), and provide a comparison to the other treatment strategies mentioned above.

## METHODS

Our study design adhered to the recommendations of the Panel on Cost-Effectiveness in Health and Medicine [8, 9]. All relevant societal costs were included, and future costs were discounted at a rate of 3%. Since there is considerable uncertainty surrounding the real world value for various parameters used in the analysis, we employed various sensitivity analysis techniques. The sensitivity analysis informs

the reader of the effect incorrect estimates of a variable or differences in infection rates between various immigrant groups might have on the incremental cost-effectiveness ratios. For simplicity, all foreign-born persons are referred to as immigrants, regardless of documentation or worker status.

## Prevalence

The prevalence of parasitosis among immigrants to the United States was obtained from the medical literature and from refugee and immigrant health clinics [10–16]. The prevalence data we used were based on a standard single stool ova and parasite examination, which has an average test sensitivity value of approximately 25% [17, 18]. The adjusted prevalence of *S. stercoralis* among immigrants was then calculated by dividing the proportionate prevalence value for a given immigrant population by the test sensitivity.

## Morbidity and mortality

To calculate life expectancy for immigrants, we first generated abridged life tables using data from the National Centre for Health Statistics for year 2000. Because immigrants are born outside the United States by definition, these life tables reflect life expectancy starting at age 1 year.

Deaths due to *S. stercoralis* [International Classification of Disease, 9th Revision (ICD-9) code 127.2] were obtained from the 1979–1998 combined mortality data file for California and New York – two states with large immigrant populations in which *S. stercoralis* is not endemic [19]. The probability of mortality was calculated as follows:

$$D/(P \cdot I),$$

where  $D$ =deaths due to *S. stercoralis*,  $I$ =the 1990 immigrant population of these states, and  $P$ =the overall prevalence of parasitosis in immigrants [20]. In this case, the 1990 immigrant population was used because it fell approximately mid-point between initial and final years of the death data file.

The number of hospitalizations due to *S. stercoralis* was obtained using 1996–2000 data from the State-wide Planning and Regional Cooperative System (SPARCS), a dataset containing billing, demographic, and diagnosis data for all civilian hospitalizations

Table 1. Selected parameters included in the decision analysis model\*

	Base	High	Low	Ref.
Cost per patient (\$2000)				
Mean cost of hospitalization†	\$13 109	\$30 400	\$8000	[21, 34]
Cost of outpatient visit†	\$75	\$130	\$20	[33]
Cost of burial	\$7020	\$10 000	\$3000	[35]
Cost of 200 mg b.i.d albendazole (5 days)	\$13.24	\$15.00	\$2.00‡	[32]
Cost of 200 mg b.i.d. albendazole (3 days)	\$7.94	\$9.00	\$1.33‡	[32]
Cost of 12 mg ivermectin once	\$21.76	\$22.00	\$5‡	[32]
Probabilities				
Discount rate	0.03	0.06	0.0	[8]
Probability of infection	0.10	0.02	0.2	[10–18]
Effectiveness of albendazole (3 days)	60 %	80 %	40 %	[25–28]
Effectiveness of albendazole (5 days)	80 %	90 %	60 %	[25, 26]
Effectiveness of ivermectin	92 %	99 %	80 %	[25, 26]
Sensitivity of eosinophilia	80 %	90 %	40 %	[27, 28]
Specificity of eosinophilia	25 %	50 %	2 %	[27, 28]
Probability of mortality†	$6.48 \times 10^{-5}$	0.00006	$6.48 \times 10^{-5}$	[19, 20]
Probability of hospitalization†§	0.000023	0.0002	0.000023	[20, 21]
Probability of outpatient visit†	0.000425	0.004	0.000425	[22]
Health-related quality of life (HRQL)				
Well	1	1	0.84	[23]
Infected, ambulatory	0.919	1	0.7	[23]
Infected, hospitalized	0.799	0.9	0.5	[23]

\* For a full list of parameters, including age-specific mortality rates, visit <http://www.pceo.org/parasitecea.html>.

† Among infected persons.

‡ Used to determine threshold cost. Medications are available overseas for less than low value.

§ Annual risk among infected persons.

in New York State [21]. Hospitalization rates were calculated as follows:

$$H/(I \cdot P),$$

where  $H$  is the average annual number of hospitalizations for *S. stercoralis* from 1996 to 2000,  $I$  is the 1998 immigrant population, and  $P$  is the prevalence of *S. stercoralis*.

The number of outpatient visits to health-care providers was calculated from Medicaid claims data from 1992 to 1996 [22]. More recent data were unavailable due to a 1996 federal law preventing recent immigrants from using most Medicaid services. The mean annual number of outpatient visits was divided by the proportion of immigrants receiving Medicaid throughout those years.

Estimates of the Health-related quality of life (HRQL) scores for various health states were derived using the Health Utilities Index 2 (HUI-2), which is a multi-attribute health status classification system used to translate dimensions of a disease into a quality adjusted life years (QALY)-compatible HRQL score

[23]. Domains include sensation, mobility, cognitive function, self-care, and pain among others. Inputs were obtained by asking two infectious disease experts familiar with *S. stercoralis* to rate each scale.

### Efficacy

Most efficacy trials of anti-parasitic agents are conducted overseas and are complicated by the potential for re-infection and the use of insensitive tests to identify infection. Determination of the sensitivity of eosinophilia for *S. stercoralis* infection is limited by the lack of a gold standard comparator and a paucity of studies. Finally, since eosinophilia occurs in the presence of many parasitic infections (as well as other medical conditions), the specificity of the test is dependent on the prevalence of other conditions in a given cohort. We, therefore, used mean values for sensitivity and specificity for eosinophilia and efficacy estimates for albendazole and ivermectin from the medical literature and tested these in a broad sensitivity analyses (see Table 1) [24–31].

Table 2. Assumptions and issues in deriving parameter estimates

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- The 1990 immigrant population is equal to the midpoint 1979–1998 population
  - It was necessary to aggregate mortality data for *S. stercoralis* over many years to obtain a large number of deaths in the numerator of mortality ratios
  - Vital statistics and hospitalization data correctly tabulate mortality and hospitalization rates due to *S. stercoralis*
  - Most cases are not likely to be identified, resulting in undercounts of deaths and hospitalizations. This assumption was tested in a broad sensitivity analysis
  - The exclusion of parasites other than *S. stercoralis* will not substantially alter cost-effectiveness ratios in populations at known risk of this parasite
  - We examined only costs and benefits associated with screening and treating *S. stercoralis*. Unlike albendazole, ivermectin does not treat hookworm, *G. lamblia*, *O. viverrini*, or *T. solium*. However, the mortality due to *G. lamblia* is extremely low, *O. viverrini* is rare, and considerable debate exists over whether albendazole would produce benefits for persons infected with *T. solium*
  - The HRQL of uninfected immigrants is 1·0
  - We tested this assumption in a sensitivity analysis varying from the mean HRQL of native-born persons to 1·0
  - Clinicians will use 12 mg ivermectin to treat patients with eosinophilia among populations at risk for *S. stercoralis*
  - *S. stercoralis* is the most dangerous parasite and ivermectin is the most effective medication. Some infectious disease specialists may opt to use a higher dose and spaced dosing to maximize efficacy, which would decrease the cost-effectiveness of this option
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### Costs

The cost of ivermectin was based on a single dose of 12 mg (approximately 200 µg/kg for a 60 kg adult), and the cost of albendazole was based on a twice-daily dose of 200 mg for either 3 or 5 days. Each cost was obtained from the 2000 Red Book, which reports average wholesale prices for medications [32]. The median cost of medical visits were estimated using 2000 data from the Medical Care Expenditure Panel Survey (MEPS), an annual survey of approximately 40 000 households that is representative of the US population as a whole. We used the median cost since data for *S. stercoralis* were not available and since a medical visit for this condition is likely to fall in the middle range of duration. Details of the survey, including imputation methods, are available from the Agency for Health Research and Quality [33].

The median cost of a hospitalization for *S. stercoralis* was obtained using charge data from SPARCS for admissions with ICD-9 code 127.2 listed as a primary diagnosis [21]. These figures were then adjusted using the cost-to-charge ratio for ‘other infectious and parasitic diseases’ (Diagnosis-Related Group 423, which includes helmenthiasis), which was derived from the Centers for Medicare and Medicaid Services (CMS) [34]. This cost-to-charge ratio was calculated by dividing the amount reimbursed by CMS by the total charges to CMS. Burial costs were added for all deaths, regardless of cause, since burial costs associated with premature death were expected to be relevant after discounting future costs [35]. The

HUI-2 does not include costs due to lost productivity; however, we chose to exclude these costs because we felt that they would be small relative to the actual cost of care.

### Decision analysis model

We developed a Markov model using DATA professional (version 4.0, TreeAge Software, Williamstown, MA, USA) that compared: (1) treating all immigrants with 200 mg albendazole twice a day for either 3 days or 5 days, (2) treating all immigrants with 12 mg ivermectin in a single dose (approximately 200 µg/kg for a 60 kg adult), (3) treating only those immigrants with documented eosinophilia with 12 mg ivermectin, and (4) watchful waiting. In our model, subjects are exposed to the annual age-specific probability of death for immigrants due to all causes; the crude mortality rate for *S. stercoralis* infection was subtracted for uninfected or successfully treated subjects. Each surviving subject is assigned a discounted HRQL value or cost for each year of life. Burial costs are incurred whenever subjects die. All assumptions of the analysis are listed in Table 2 and all parameter values are listed in Table 1.

In the model, patients are assigned to a state of being either infected with *S. stercoralis* or uninfected. In treatment arms, the probability of infection is equal to the product of the parasitic prevalence and the efficacy of the medication administered. In the eosinophilia arm, subjects are allocated to receive treatment or no treatment by infection status using the prevalence, sensitivity, and specificity of the test.

Table 3. Cost, incremental cost, effectiveness, incremental effectiveness, and incremental cost-effectiveness per QALY gained of all strategies evaluated at various prevalence ratios (negative values)

Strategy	Cost	Incremental cost	Effectiveness	Incremental effectiveness	Incremental cost-effectiveness	Incremental cost-effectiveness WW*
2% Prevalence						
Watchful waiting	\$1666	—	25·91 QALYs	—	—	—
Albendazole (3 days)	\$1674	\$8	25·92 QALYs	0·0050 QALYs	\$1584	\$1584
Albendazole (5 days)	\$1680	\$5	25·92 QALYs	0·0017 QALYs	\$3175	\$1982
Eosinophil screening	\$1684	\$4	25·92 QALYs	(0·0006 QALYs)	Dominated†	Dominated†
Ivermectin (once)	\$1688	\$9	25·92 QALYs	0·0010 QALYs	\$8514	\$2834
10% Prevalence						
Watchful waiting	\$1666	—	25·88 QALYs	—	—	—
Albendazole (3 days)	\$1674	\$8	25·90 QALYs	0·0250 QALYs	\$314	\$314
Albendazole (5 days)	\$1680	\$5	25·91 QALYs	0·0083 QALYs	\$632	\$393
Eosinophil screening	\$1684	\$4	25·91 QALYs	(0·0029 QALYs)	Dominated†	Dominated†
Ivermectin (once)	\$1688	\$9	25·92 QALYs	0·0050 QALYs	\$1700	\$564
20% Prevalence						
Watchful waiting	\$1667	—	25·84 QALYs	—	—	—
Albendazole (3 days)	\$1674	\$8	25·89 QALYs	0·0500 QALYs	\$155	\$155
Albendazole (5 days)	\$1680	\$5	25·90 QALYs	0·0167 QALYs	\$314	\$195
Eosinophil screening	\$1684	\$4	25·90 QALYs	(0·0057 QALYs)	Dominated†	Dominated†
Ivermectin (once)	\$1688	\$8	25·91 QALYs	0·0100 QALYs	\$848	\$280

\* Relative to watchful waiting.

† Dominated strategies are both more expensive and less effective than others.

The variables used in our analyses were subjected to a Monte Carlo simulation and to a series of one-way and two-way sensitivity analyses. In a one-way analysis, all variables are held constant but one. In a Monte Carlo simulation, values for all variables are sampled from a statistical distribution. In our Monte Carlo simulation, we used a triangular distribution [36]. In this distribution, the base-case estimate is entered as the most likely value, and the likelihood of values between this value and the high and low value are linearly interpolated.

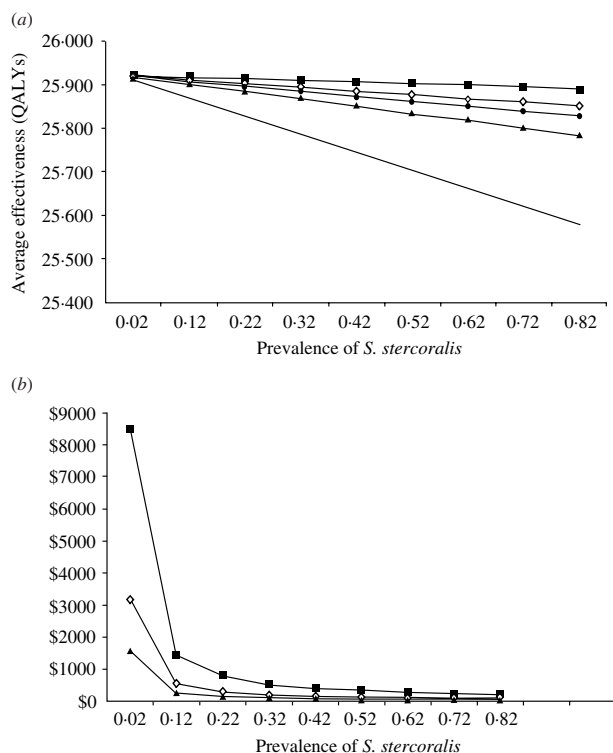
## RESULTS

Table 3 presents the results of the cost-effectiveness analysis at a 2, 10, and 20% prevalence of *S. stercoralis* infection. When the prevalence of *S. stercoralis* is 10% (a rate commonly seen in mixed refugee screening settings), presumptive treatment with 200 mg albendazole, twice a day over 3 days, was associated with an incremental cost-effectiveness ratio of \$314 per QALY gained relative to watchful waiting. The presumptive treatment of immigrants at risk of parasitosis with 5 days of albendazole may be desired to ensure better coverage of *S. stercoralis* as well as other parasitic infections such as *Giardia lamblia*.

This option is associated with an incremental cost-effectiveness ratio of \$632 relative to 3 days of albendazole and \$393 relative to watchful waiting. Optimal coverage of *S. stercoralis* can be achieved with ivermectin. Presumptive treatment with 12 mg ivermectin in a single dose was associated with a cost of \$1700 per QALY gained relative to treatment with 5 days of albendazole and \$564 per QALY gained relative to watchful waiting. Regardless of the prevalence, the strategy of basing treatment on previously known eosinophil results (i.e. excluding the cost of a complete blood count with differential) was both more expensive and less effective than other options (dominated).

The Figure presents mean effectiveness and incremental cost-effectiveness ratios of the treatment strategies at various prevalence ratios of *S. stercoralis* infection. Presumptive treatment of immigrants with ivermectin increases incremental cost-effectiveness alongside prevalence ratios, with maximal cost-effectiveness when prevalence ratios are greater than 10–12%. Over the range of prevalence values examined, none of the presumptive treatment strategies was clearly preferred over another.

All variables listed in Table 1 were tested in one-way and Monte Carlo sensitivity analyses. Changes in



**Fig.** Effectiveness and incremental cost-effectiveness of the strategies under evaluation. Ivermectin is the most effective strategy across the prevalence ratios of *S. stercoralis* (a). —■—, Ivermectin (1 day); —◇—, albendazole (5 days); —▲—, albendazole (3 days); —●—, eosinophil; —, nothing. However, it is more expensive than other strategies (b). Dominated options are not shown in panel (b).

the efficacy of the regimens over plausible values exerted only a moderate effect on the relative ranking of each regimen, and changes in other variables had no substantive effect on strategy rankings. Notable analyses that exerted little effect on the model include the discount rate, the cost and probability of medical events, and state-specific HRQL scores. In Monte Carlo analyses, all three presumptive treatment strategies overlapped considerably. Any given strategy exceeded \$50 000 in less than 1% of all trials.

**DISCUSSION**

In our analysis we found that ivermectin was a more effective strategy, but was also an incrementally more expensive (per QALY gained) than albendazole for the treatment of *S. stercoralis* infections in new immigrants to the United States. The additional expense of ivermectin was \$1700 per QALY gained, a very small cost relative to most other medical interventions in the United States. Across prevalence ratios

commonly seen in immigrant groups, the cost of presumptive treatment is significantly less than the cost of treatment of essential hypertension in 20-year-old males vs. no treatment, or the nicotine patch for 25-year-old smokers vs. no treatment [37]. While the incremental cost-effectiveness of ivermectin was dependent upon the underlying prevalence of *S. stercoralis* infection, no one strategy clearly dominated the other.

In evaluating the use of eosinophil counts to guide presumptive treatment, we used a high estimate of test sensitivity, a generous specificity, and did not include the cost of a CBC with differential in the analysis. All of this increases the likelihood of a finding in favour of incorporating eosinophilia data; nonetheless the strategy was dominated. Though the positive predictive value of eosinophilia increases with increasing parasite prevalence, this strategy becomes more costly and less effective than the other options as prevalence increases. This is attributable to increasing false-negative test results. While the test has a higher positive predictive value when all intestinal parasites that cause eosinophilia are considered together, other parasites are infrequently fatal and generate fewer costs than *S. stercoralis*. It is, therefore, unlikely that adding other intestinal helminths to the model (with concomitant improvements in specificity) would greatly improve the incremental cost-effectiveness of this option.

The prevalence of *S. stercoralis* varies considerably by region of the world and the subpopulation sampled. For example, Gyorkos et al. [38] conducted a serosurvey for *S. stercoralis* among Southeast Asians immigrating to Canada and reported that Cambodians had a seroprevalence of 76.6%, Laotians had a seroprevalence of 55.6%, and Vietnamese had a seroprevalence of 11.8%. Serology indicates both active and previous infections and may produce an overestimate of the prevalence of *S. stercoralis*. Nonetheless, these numbers underscore the heterogeneity of infection rates among different groups; predominately high-risk refugees screened with 1–3 stool ova and parasite examinations in Texas and Minnesota have an average uncorrected infection rate of 1.8–4% (or approximately 3–12% after correction for the sensitivity of the stool ova and parasite examination) [39, 40]. We demonstrate that presumptive treatment is cost-effective across a wide range of prevalence values. Clinics that treat refugees and immigrants may wish to use our data to tailor treatment after considering the prevalence of infection

in the population they treat, the mix of parasites in the population they treat, and budgetary concerns.

For instance, albendazole has a broader spectrum of action and includes activity against hookworm and *G. lamblia*, as well as certain flatworms. Both ivermectin and albendazole provide coverage of other infections as well, including *Ascaris lubricoides*, *Trichuris trichiura*, and certain forms of filariasis [41]. While estimating the morbidity or costs associated with administering albendazole for some of these organisms is limited by inadequate data, short-term clinical and public health benefits may be realized from the presumptive treatment of immigrant and refugee populations using broad spectrum anti-parasitic medications. However, the elimination of *S. stercoralis* should be prioritized in populations in whom this parasite is prevalent given its potential for life-threatening illness and capacity for auto-infection.

Our inability to capture the costs and benefits of presumptively treating these other parasites is a limitation of this study. Including them would probably improve the incremental cost-effectiveness of 5 days of albendazole relative to 3 days of albendazole treatment or ivermectin. It would also slightly improve the incremental cost-effectiveness of eosinophil screening. Another limitation is the use of billing and vital-statistics data to capture the morbidity and mortality associated with *S. stercoralis*. Contributing to misclassification bias in datasets is clinicians' unfamiliarity with the disease and the lack of a sensitive diagnostic test. Even tuberculosis, a condition that is probably more familiar to clinicians, is correctly classified on death certificates just 34% of the time [42]. Misclassification bias probably results in an underestimate of medical visits and deaths due to this parasite but would not substantially affect the rank order of the modalities.

Finally, we were unable to evaluate all possible screening and treatment strategies. Strategies for selecting persons at risk for *S. stercoralis* include stool ova and parasite screening, obtaining eosinophil counts [43], asking patients about rural or urban residence [44], screening for the presence of asthma-like respiratory symptoms [45] and serological screening tests [46]. While stool screening examinations [4] and treatment contingent on known eosinophil counts are more expensive and less effective than presumptive treatment, there are insufficient data to evaluate the other options. Serological screening is much more sensitive than stool screening, however

the cost and positive predictive value of this option render it an unlikely addition to the arsenal of cost-effective preventive modalities. One option in need of evaluation is screening based on urban or rural residence in the country of origin. Knowledge of the prior probability of infection could greatly reduce the number of uninfected persons who would otherwise receive treatment.

Alternative treatment options exist as well. For instance, ivermectin has been combined with albendazole in some international studies [47, 48]. We did not evaluate this approach as a policy due to concerns surrounding the possibility of drug interactions.

It is also prudent to limit presumptive treatment to those for whom the drugs have demonstrated safety. Ivermectin and albendazole are pregnancy category C drugs [30, 31].

The present analysis improves upon an earlier study [4]. In addition to improving mortality and hospitalization rate estimates by using multiple years of data, it uses a Markov model and includes additional preventive strategies. Using a deterministic model and discounted lifetime probabilities of hospitalization and death, that study biased all variables against presumptive treatment, evaluated multiple parasites, and found cost savings associated with presumptive treatment with 5 days of albendazole. The cost savings realized by that study were attributable to slightly higher hospitalization and mortality estimates for *S. stercoralis* (due to random error associated with the use of a single year of data) and the inclusion of four parasites rather than one. Though the present analysis demonstrates that treatment may be associated with costs, it should be emphasized that the number of deaths and hospitalizations in the real world are likely to be substantially higher than reported in national datasets. Therefore, the costs averted by treatment are likely to be substantially higher.

Immigrants from Eastern Europe, Asia, Africa, Latin America, and the Middle East are all at risk of parasitosis, but there is considerable variability even within these groups. The ideal management of parasitic infections in immigrant populations might consider the population's risk of infection with *S. stercoralis* relative to other parasites. Many institutions, such as most federal refugee health clinics, have these data. By combining our analysis with nation-specific data on the prevalence of *S. stercoralis* infections, providers should be able to maximize the quality and quantity of life of their immigrant populations within their own budgetary constraints.

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