Vaccine 37 (2019) 3704–3714

Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

Economic value of a therapeutic Chagas vaccine for indeterminate and Chagasic cardiomyopathy patients

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ARTICLE INFO

Article history:
Received 4 January 2019
Received in revised form 6 May 2019
Accepted 9 May 2019
Available online 16 May 2019

ABSTRACT

Background: Therapeutic vaccines to prevent Chagas disease progression to cardiomyopathy are under development because the only available medications (benznidazole and nifurtimox) are limited by their efficacy, long treatment course, and side effects. Better understanding the potential clinical and economic value of such vaccines can help guide development and implementation.

Methods: We developed a computational Chagas Markov model to evaluate the clinical and economic value of a therapeutic vaccine given in conjunction with benznidazole in indeterminate and chronic Chagas patients. Scenarios explored the vaccine's impact on reducing drug treatment dosage, duration, and adverse events, and risk of disease progression.

Results: When administering standard-of-care benznidazole to 1000 indeterminate patients, 148 discontinued treatment and 219 progressed to chronic disease, resulting in 119 Chagas-related deaths and 2293 DALYs, costing $18.9 million in lifetime societal costs. Compared to benznidazole-only, therapeutic vaccination administered with benznidazole (25–75% reduction in standard dose and duration), resulted in 37–111 more patients (of 1000) completing treatment, preventing 11–219 patients from progressing, 6–120 deaths, and 108–2229 DALYs (5–100% progression risk reduction), saving ≤$16,171 per patient. When vaccinating determinate Kuschnir class 1 Chagas patients, 10–197 fewer patients further progressed compared to benznidazole-only, averting 11–228 deaths and 144–3037 DALYs (5–100% progression risk reduction), saving ≤$34,059 per person. When vaccinating Kuschnir class 2 patients, 13–279 fewer progressed (279 with benznidazole-only), averting 13–692 deaths and 283–10,785 DALYs (5–100% progression risk reduction), saving ≤$89,759. Therapeutic vaccination was dominant (saved costs and provided health benefits) with ≥ 5% progression risk reduction, except when only reducing drug treatment regimen and adverse events, but remained cost-effective when costing <$200.

Conclusions: Our study helps outline the thresholds at which a therapeutic Chagas vaccine may be cost-effective (e.g., <5% reduction in preventing cardiac progression, 25% reduction in benznidazole treatment doses and duration) and cost-saving (e.g., ≥5% and 25%, respectively).

1. Introduction

Therapeutic vaccines to prevent Chagas disease progression to cardiomyopathy are under development because the only available medications (antitrypanosomal treatment such as benznidazole and nifurtimox) are limited by their efficacy, long treatment course, and side effects. With at least 12 therapeutic candidates in pre-clinical trials [1], decision makers (e.g., policy makers, vaccine developers, manufacturers, third-party payers, and potential funders) need to understand the potential clinical and economic value of such a vaccine. Those infected with *Trypanosoma cruzi* may progress to severe heart disease and while the medications available to prevent this progression are effective in the early stages of Chagas infection [2], they have limited efficacy in later stages. A recent randomized clinical trial (RCT) of patients with

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https://doi.org/10.1016/j.vaccine.2019.05.028
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Chagasic cardiomyopathy failed to show any improvement in cardiac clinical outcomes and 17–18% of patients died within five years, regardless of benznidazole treatment [3]. Additionally, these medications have a treatment course up to two months and are highly toxic, with adverse reactions in up to 40% of patients, and 20% of patients unable to tolerate a full treatment course [4].

Currently, therapeutic vaccines, either used alone or with benznidazole in a vaccine-linked chemotherapy approach, are the most desired and feasible development strategy to overcoming current treatment deficiencies [1,4]. Pre-clinical trials in mice have demonstrated reductions in parasite heart burdens and cardiac fibrosis and pathology [5–10]. Besides delaying the onset of clinical cardiac outcomes, vaccination could also reduce chemotherapy duration and dosage, leading to higher treatment completion rates [4]. While our previous work evaluated a Chagas therapeutic vaccine for intermediate patients, it explored only vaccination and its impact on delaying cardiac outcomes [11]. Here, we evaluate administering the vaccine in conjunction with benznidazole (accounting for reductions in drug regimen and progression of disease) and in patients with indeterminant and chronic disease. With therapeutic vaccines in the pipeline, evaluating the economic value prior to licensure can help guide development and implementation, determine appropriate target populations, desired efficacy profiles, and vaccine price points [12–14]. Therefore, we developed a computational simulation Markov model to determine the economic value of a therapeutic vaccine (given in combination with benznidazole) for Chagas patients in Mexico at different stages of disease to improve treatment completion and to prevent and delay the onset of Chagasic cardiomyopathy. We used Mexico as our test case as it has one of the largest number of persons living with Chagas disease and cardiomyopathy [15,16].

2. Methods

2.1. Model

Using TreeAge Pro 2017 (Williamstown, MA), we developed a computational Markov model of Chagas disease to evaluate the use of vaccine-linked chemotherapy from the third-party payer and societal perspectives. Our model consisted of six mutually exclusive states (four clinical classes, successfully treated/seroreverted, and death; Fig. 1). The four clinical classes followed the Kuschnir Classification system [17]: class 0 [i.e., reactive serology, normal echocardiogram (ECG), and no cardiac enlargement]; class 1 (i.e., reactive serology, abnormal ECG, and no cardiac enlargement); class 2 (i.e., reactive serology, abnormal ECG, cardiac enlargement, and no signs of heart failure); and class 3 (i.e., heart failure). Each clinical class was associated with different costs and health effects.

All patients entered the model before the onset of heart failure (i.e., start in Kuschnir class 0, 1, or 2), thus, they had either indeterminate Chagas disease (i.e., Kuschnir class 0) or determinate Chagas disease with early-stage evidence of cardiac clinical manifestations (i.e., Kuschnir class 1 or 2). During the first year, patients received either standard-of-care with benznidazole only (5 mg/kg per day for 60 days) or care with benznidazole plus therapeutic vaccination (i.e., vaccine-linked chemotherapy). Treatment with benznidazole was associated with a probability of discontinuation due to side effects (i.e., treatment is not completed) and we assumed treatment would not be effective at preventing the progression of cardiac disease. Treatment was also associated with a probability of interruption due to side effects; we assumed these patients were treated with antihistamines or other measures and eventually completed the full treatment course. Patients completing treatment had a probability of successful treatment (i.e., will serorevert), which was associated with a duration until seroreversion. These patients cycled in the model until this duration elapsed, before moving into the successful treatment state, thus leaving the model. Vaccination reduced the following, depending on the scenario: dosage and duration of benznidazole treatment, probability of side effects, and probability of disease progression and Chagas-related mortality (i.e., movement into another Kuschnir class or mortality in class vaccinated in if no progression). By reducing the probability of progression, vaccination delays the onset of cardiac outcomes. The vaccine's duration of action determined how long (i.e., number of years) the progression risk was attenuated. After this duration elapsed, a Chagas patient could receive a booster (incurring the cost of the vaccine), continuing to reduce progression risk. Additionally, vaccination was associated with a probability of side effects.

The model had a one-year cycle length. At the end of each year, patients could stay in the same state or move to any other state. Patients who moved between clinical classes, did so based on the annual probability of progression. Patients could progress through multiple classes during the course of the year (i.e., one cycle), accounting for the rapid onset of some clinical symptoms observed in some Chagas patients. In subsequent years, patients received annual care for Chagas disease, which included check-ups (i.e., medical counseling), laboratory testing, imaging, hospitalization, and other medications. Hospitalization duration varied by level of care and if the patient had congestive heart failure (CHF). Additionally, each year, patients had probabilities of developing other clinical outcomes, including stroke (could occur in any Kuschnir class) and having a pacemaker or cardio-defibrillator implanted (could occur in Kuschnir classes 1–3). The model ran for 100 cycles or until all individuals entered the death state. We applied a half-cycle correction to account for events occurring at any point during the year.

2.2. Simulations and model outcomes

Each simulation sent 1000 Chagas patients through the model 1000 times (total of 1 million trials with unique outcomes). For each simulation, we calculated the incremental cost-effectiveness ratio (ICER) as:

$$\text{ICER} = \left(\text{Cost}_{\text{Vaccine plus Benznidazole}} - \text{Cost}_{\text{Benznidazole}}\right) / \left(\text{Health Effects}_{\text{Benznidazole}} - \text{Health Effects}_{\text{Vaccine plus Benznidazole}}\right)$$

where health effects were measured in disability-adjusted life years (DALYs) and deaths. DALYs are the sum of the years of life lived with disability (YLD) and years of life lost (YLL) due to Chagas-related deaths. YLL and YLD are calculated as:

$$\text{YLD} = \text{Number of Incident Cases} * \text{Disability Weight} * \text{Average Duration in Years}$$

$$\text{YLL} = \text{Number of Deaths} * \text{Life Expectancy at Age of Death in Years}$$

The third-party payer or health system perspective included all direct medical (e.g., annual care and hospitalization) costs, while the societal perspective included direct and indirect (e.g., productivity losses due to absenteeism and mortality) costs. The cost per hospital bed day and duration of hospitalization were used to estimate hospitalization costs. Daily income served as a proxy for productivity losses associated with absenteeism (which varied by disease state) and mortality. A Chagas-specific premature death resulted in accruing the net present value (NPV) of that person's lifetime earnings, based on their age at death and remaining life years based on life expectancy. All costs are in 2018 $US, with all

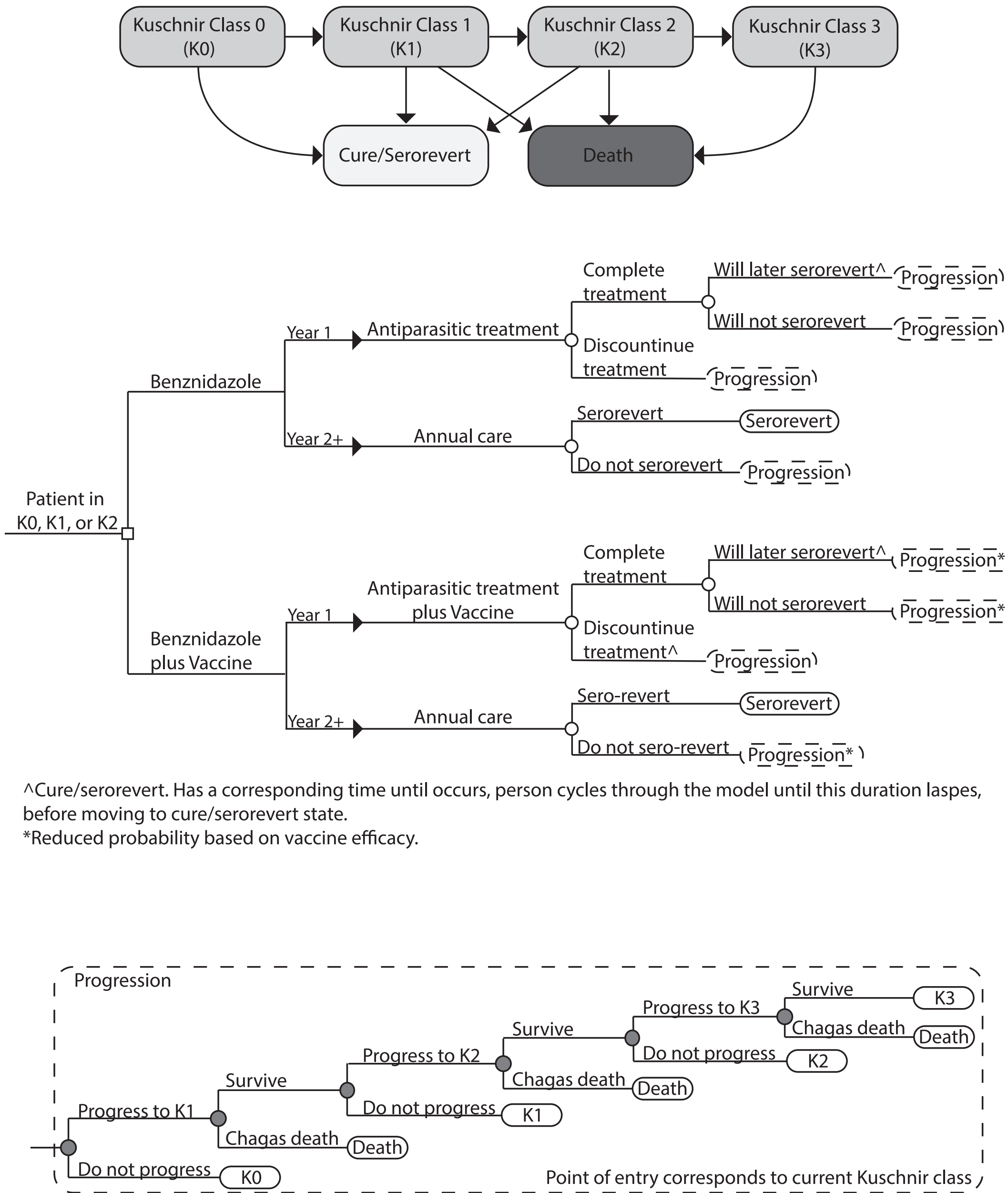

Fig. 1. Markov model outline and patient flow through model.

past and future values discounted with a 3% rate. Similarly, all future DALYs are presented in NPV, discounted with a 3% rate. Vaccination was considered highly cost-effective if less than Mexico's gross domestic product (GDP) per capita [i.e., $8709 using exchange rates and $19,216 using purchasing power parity (PPP) [18]]; cost-effective if 1–3 times the GDP, and not cost-effective if > 3 times the GDP.

2.3. Data sources

Table 1 shows the model input parameters, values, and sources. All data came from the scientific literature or international databases and was Chagas-specific when available, with a preference for data from Mexico. When converting costs between currencies, we discounted costs and then converted into US dollars using two conversion methods. The first used the exchange rate (18.6 pesos/dollar, which was the average for 2018 as of March 18th [19]) where we discounted costs to 2018 values before conversion; the second used the PPP conversion factor (9.230019 for 2017 [20]) where we discounted costs to 2017 values, converted to international dollars, converted to US dollars, then discounted to 2018 values. Daily income came from the reported national quarterly income which includes other benefits (e.g., fringe benefits, pensions) in addition to formal wages. The cost per hospital bed day came from the National Institute of Medical Sciences and Nutrition, focused on the cost for the government sector (which provides healthcare for most Chagas cases in Mexico), and used the real price of the service or attention [22]. We used the mean hospitalization days per year per patient reported for Chagas patients in Columbia [23]. In addition, a one-day hospital stay was applied for each procedure, so that the total costs for cardiac procedures included the procedure itself, the device, and one bed day. Life expectancy data and the annual probability of mortality came from the World Health Organization Global Health Observatory [24].

Table 1
Model input parameters, values, and sources.

Parameter	Distribution Type	Mean or Median	Standard Deviation or Range	Source(s)
Costs (2018 $US)				
Antihistamines	Triangular	2.19	0.77 – 5.25	[43]
Minor vaccine side effects (paracetamol)	Triangular	2.17	1.31–2.51	[43]
Annual care^				
Indeterminate disease	Point Estimate	59.11		[44]
No CHF	Point Estimate	204.73		[44]
Cardiomyopathy with CHF	Point Estimate	1168.38		[44]
Benznidazole (100 mg)	Uniform		0.128–0.313	[45]
Daily income (exchange rate method)§ (percent population)	Point Estimate	23.54		[21]
Daily income (PPP method)§	Point Estimate	47.44		[21]
Hospital bed day (exchange rate method)§§	Point Estimate	142.68		[22]
Hospital bed day (PPP method)§§	Point Estimate	287.53		[22]
Pacemaker implant (exchange rate method)	Point Estimate	727.40		[46]
Pacemaker implant (PPP method)	Point Estimate	1465.83		[46]
Automatic cardioverter/defibrillator implant (exchange rate method)	Point Estimate	772.23		[46]
Automatic cardioverter/defibrillator implant (PPP method)	Point Estimate	1556.18		[46]
Stroke (first time)	Point Estimate	4945.47		[47]
Probabilities (annual)				
Discontinue benznidazole treatment	Uniform		0.12–0.18	[48]
Interrupt benznidazole treatment	Beta	0.1125	0.0106	[3,27]
Successful treatment/serorevert due to drug treatment (one time probability)	Beta	0.1688	0.0312	[26,27]
Minor vaccine side effects	Point Estimate	0.27		[49,50]
Intermediate level care	Point Estimate	0.778		[23]
Specific level care	Point Estimate	0.222		[23]
Progress to Kuschnir class 1 (lifetime)†	Uniform		0.2–0.3	[2,29]
Progress to Kuschnir class 2	Point Estimate	0.2		Calibrated
Progress to Kuschnir class 3	Point Estimate	0.3		Calibrated
Incidence of stroke (per 100 patients per year)	Point Estimate	2.7		[2,51]
Chagas-related mortality				
Kuschnir class 1	Point Estimate	0.005		[28,52,53]
Kuschnir class 2	Beta	0.0601	0.0364	[54]
Kuschnir class 3	Beta	0.0868	0.0629	[54]
Pacemaker	Beta	0.0224	0.0209	[3,23,26,56–58]
Cardioverter defibrillator	Beta	0.00247	0.00163	[3,23,56,57]
Durations and Numbers				
Time in indeterminate stage (years)†	Uniform		5–10	Assumption, [2,29,58]
Patient starting age (years)	Triangular	38	28–48	Assumption
Time until test negative (years)	Triangular	11.7	5.9–15.7	[26,27]
Lost productivity (days)				
Indeterminate	Point Estimate	5		[59]
Cardiomyopathy	Point Estimate	15		[59]
No CHF	Point Estimate	14		[44]
Hospitalization (days)				
Intermediate level care with CHF	Point Estimate	2.6		[23]
Specific level care with CHF	Point Estimate	14.2		[23]
Intermediate care without CHF	Point Estimate	1		[23]
Specific level care without CHF	Point Estimate	6.8		[23]
For cardiac procedure	Point Estimate	1		Expert Opinion
*Disability Weights**				
Cardiac conduction disorders (Kuschnir class 1)	Triangular	0.224	0.151–0.312	[25]
Angina pectoris (Kuschnir class 2)	Triangular	0.08	0.052–0.113	[25]
Heart failure (Kuschnir class 3)	Triangular	0.179	0.122–0.251	[25]
Stroke	Triangular	0.07	0.046 – 0.99	[25]

CHF = congestive heart failure; PPP = purchasing power parity. Calibrated values such that overall 20–30% of those with indeterminate disease develop chronic disease and 10–15% develop heart failure.
^ Includes annual check-ups (medical counseling, labs, and imaging), and other drugs if appropriate.
§ Value includes fringe benefits and other income sources (e.g., pensions) as reported by the National Survey on Household Income and Expenditure (ENIGH) as it incorporates additional income beyond formal wages.
§§ Used real price of the service or attention (i.e., level 6).
† Based on likelihood of progression from indeterminate to chronic disease over 10–20 years; duration reduced to account for patient age and time already spent in indeterminate stage.
* Kuschnir class 1 assumes weight for cardiac conduction disorders and cardiac dysrhythmias; Kuschnir class 2 assumes weight for angina pectoris: moderate; Kuschnir class 3 assumes heart failure: severe; stroke assumes stroke: long-term consequences, moderate.

Economic data (GDP) came from the World Bank [18]. Disability weight values for Chagas-associated health outcomes came from the Global Burden of Disease 2015 [25].

Data on the probability of successful treatment/seroreversion and duration until seroreversion came from clinical trials [26,27]. Due to lack of robust data in the literature [26–28], the probabilities for progression through the Kuschnir classes were calibrated so that 20–30% of indeterminate patients develop chronic infection [2,29] and 10–15% developed heart failure (i.e., progressed to Kuschnir class 3).

2.4. Sensitivity analyses

Probabilistic sensitivity analyses (i.e., Monte Carlo simulations) varied each parameter throughout its ranges in Table 1. Sensitivity analyses varied vaccine cost ($50-$200), vaccine duration of action (10 years to lifelong), the reduction in drug treatment duration (15–45 days), dosage (25–75%), and adverse drug reactions (25–75%), and the probability of progressing and reducing Chagas-related mortality (0–100%), the cost of a bed day (0–20% higher), and the duration of hospitalization (±50%). Additional scenarios evaluated the vaccine with and without a booster.

3. Results

3.1. Vaccination of patients with indeterminate Chagas disease (Kuschnir class 0)

Table 2 shows the impact of vaccine-linked chemotherapy and disease progression per 1000 indeterminate Chagas patients for a lower, moderate, and higher impact lifelong vaccine, as well as the Chagas outcomes for non-vaccinated patients. With benznidazole-only treatment, 219 [95% uncertainty interval (UI): 191–248] Chagas patients progressed to chronic disease, resulting in 119 Chagas-related deaths (4 in class 1, 10 in class 2, and 105 in class 3) over their lifetime. Compared to benznidazole-only treatment, therapeutic vaccination prevented 43 to 176 patients (of 1000 treated) from progressing to Kuschnir class 1 and subsequently, 24 to 96 Chagas-related deaths, averting 449.5 to 1810.7 DALYs, varying from 20% to 80% reduction in progression (Table 2). Fig. 2 shows the cost-savings per person for therapeutic vaccination.

Therapeutic vaccination was economically dominant (i.e., saved costs and provided health benefits) compared to benznidazole-only treatment from both perspectives, when reducing the progression risk by ≥ 5% (vaccine cost ≤$100). A $200 vaccine was highly cost-effective when reducing progression by 5% ($754/DALY averted; exchange rate method) and dominant when reducing progression risk by 10% from the third-party payer perspective. Therapeutic vaccination was dominant compared to benznidazole-only treatment when changing hospital duration and cost per bed day (≥20% reduction in progression risk). When completely stopping disease progression (i.e., 100% reduction in progression risk), therapeutic vaccination was dominant compared to benznidazole-only under all tested conditions, preventing 219 (95% UI: 188–248) patients from progressing to chronic disease, 120 (95% UI: 88–149) Chagas-related deaths, and averting 2217.3 to 2229.2 DALYs. Fig. 3 shows the number of Chagas-disease progressions prevented and number of Chagas-related deaths averted compared to benznidazole-only treatment when varying the reduction in the probability of disease progression. Gains in both increased linearly when further reducing disease progression risk.

Vaccination that reduced disease progression risk (20–100%) for 10 years was dominant compared to benznidazole only for costs ≤$200, regardless of if a booster was given or not. When reducing progression by 20% for 10 years (i.e., lower impact 10-year therapeutic vaccine), of 1000 treated, 44 fewer indeterminate patients progressed to chronic disease, and subsequently 12 and 11 fewer progressed to Kuschnir class 2 and class 3, respectively; averting 10 deaths, 321.6 DALYs, and saving $1623 per person (no booster, $200 vaccine, societal perspective, exchange rate method).

Even when the vaccine only reduced benznidazole treatment dosage and duration (i.e., did not reduce disease progression probability), vaccination prevented between 37 and 111 patients (per 1000 treated) from discontinuing treatment (25% to 75% reduction in adverse events) and averted up to 10.1 DALYs. While therapeutic vaccination cost $24 to $180 more per patient than benznidazole-only treatment from the third-party payer perspective (varying with vaccine cost and dosage reduction and conversion method), it was cost-effective (ICERs $1262-$23,120/DALY averted, both conversion methods), except when reducing dosage, duration, and adverse events by 25% and when costing ≥ $100 (≥$40,351/DALY averted) using the exchange rate method and when costing ≥ $200 (≥ $75,128/DALY averted) using the PPP method.

3.2. Vaccination of patients with determinate Chagas disease in Kuschnir class 1

Vaccination of Kuschnir class 1 patients prevented 37 to 157 (of 1000 treated) from progressing to worse cardiac outcomes and 43 to 181 Chagas-related deaths, averting a total of 616.4 to 2440.1 DALYs (Table 3). Therapeutic vaccination saved $31 to $766 per patient from the third-party payer perspective and $6188 to $26,710 per patient from the societal perspective compared to benznidazole-only treatment using the exchange rate method (Fig. 2). Using the PPP method, therapeutic vaccination saved $17 to $743 and $12,488 to $53,155 per patient from the third-party payer and societal perspectives, respectively, compared to benznidazole-only treatment (Fig. 2). When the vaccine prevented disease progression (100% risk reduction), 197 of 1000 treated did not progress to Kuschnir class 2, averting 229 deaths and 2978 to 3037 DALYs. Again, prevented progressions and deaths increased linearly with increases in vaccine benefits (Fig. 3).

Vaccine-linked chemotherapy for Kuschnir class 1 patients was dominant compared to benznidazole-only treatment from both perspectives when reducing the probability of progression by at least 10% for costs up to $100. A $200 vaccine becomes dominant when reducing progression by at least 20% (Table 3). When reducing progression risk by 5%, vaccination was highly cost-effective ($92-$750/DALY averted, exchange rate method) with a $100-$200 cost and dominant with a $50 cost from the third-party payer perspective. Results were robust to changes in hospitalization duration and cost per bed day.

Vaccine-linked chemotherapy with a vaccine effective for 10 years was dominant compared to benznidazole only, regardless of the probability of getting a booster, except when it cost $200 from the third-party payer perspective, where therapeutic vaccination was highly cost-effective, costing ≤$253/DALY averted (exchange rate method). Without a booster, therapeutic vaccination still prevented ≥ 9 patients from progressing to Kuschnir class 2 and ≥ 9 to Kuschnir class 3, averting ≥ 25 total Chagas-related deaths, and ≥ 387.2 DALYs.

When the vaccine did not reduce the progression of the disease, 37 to 112 fewer Chagas patients discontinued treatment (25% to 75% reduction in benznidazole treatment dosage, duration, and adverse outcomes). Therapeutic vaccination was dominant with a ≤$50 vaccination from the third-party payer perspective and a ≤$100 vaccination from the societal perspective when the vaccine had a ≥ 75% reduction in benznidazole dosage, duration, and adverse events. For all other dosage reductions, therapeutic vaccination was highly cost-effective or cost-effective, averting $61-$9,696/DALY from both perspectives for both conversion methods.

3.3. Vaccination of patients with determinate Chagas disease in Kuschnir class 2

Table 4 shows the costs and disease progression outcomes per 1000 Kuschnir class 2 Chagas patients. Overall, 37 to 111 more patients (per 1000 treated) completed treatment with vaccination

Table 2
Cost (net present value, in millions $US) and number of clinical outcomes [median (95% uncertainty interval)] among 1000 indeterminate Chagas patients treated with benznidazole and vaccine-linked chemotherapy with a lifetime duration of reducing risk of progression.

	Cost Third-Party Payer Perspective (Exchange Rate Method)	Cost Societal Perspective (Exchange Rate Method)	Cost Third-Party Payer Perspective (PPP Method)	Cost Societal Perspective (PPP Method)	Disability-Adjusted Life Years (DALYs)	Discontinue Treatment	Progress to Kuschnir Class 1	Chagas Related Death in Kuschnir Class 1	Progress to Kuschnir Class 2	Chagas Related Death in Kuschnir Class 2	Progress to Kuschnir Class 3	Chagas Related Death in Kuschnir Class 3
Drug Treatment Only												
Benznidazole	2.9 (2.2–3.4)	18.9 (13.8–24.2)	3.6 (2.8–4.6)	35.6 (26.4–46.0)	2293.1 (1625.9–2908.9)	148 (127–170)	219 (191–248)	4 (1–9)	175 (149–200)	10 (5–17)	164 (139–189)	105 (79–132)
Drug Treatment plus Vaccination												
Vaccine $50												
Lower Impact	2.5 (1.9–3.0)	15.6 (11.4–20.0)	3.1 (2.4–3.9)	29.8 (21.2–38.5)	1809.0 (1275.7–2316.1)	112 (93–130)	175 (149–200)	3 (0–7)	139 (116–162)	8 (3–15)	130 (109–153)	83 (61–107)
Moderate Impact	2.1 (1.7–2.6)	12.5 (9.0–16.2)	2.6 (2.0–3.3)	23.2 (17.0–30.2)	1386.6 (982.4–1817.5)	74 (58–91)	131 (109–154)	2 (0–6)	104 (85–124)	6 (2–11)	98 (79–118)	63 (45–82)
Higher Impact	1.4 (1.1–1.7)	6.0 (4.4–7.8)	1.6 (1.2–1.9)	10.9 (8.0–14.6)	482.4 (313.4–702.3)	37 (25–48)	43 (32–56)	1 (0–3)	34 (25–46)	2 (0–5)	32 (22–44)	20 (12–31)
Vaccine $100												
Lower Impact	2.6 (2.0–3.1)	16.0 (11.8–20.2)	3.2 (2.5–4.0)	30.0 (21.4–38.3)	1819.7 (1276.4–2331.7)	111 (91–133)	175 (148–201)	3 (0–7)	139 (115–163)	8 (3–14)	131 (108–154)	83 (60–105)
Moderate Impact	2.2 (1.8–2.7)	12.5 (9.1–16.1)	2.6 (2.0–3.3)	23.6 (17.2–30.8)	1376.7 (995.2–1819.5)	74 (59–89)	131 (109–156)	2 (0–7)	104 (86–126)	6 (2–11)	98 (80–119)	62 (45–81)
Higher Impact	1.5 (1.2–1.7)	6.1 (4.4–7.9)	1.6 (1.3–2.0)	11.0 (8.1–14.6)	495.4 (305.7–709.2)	37 (26–50)	44 (31–57)	1 (0–3)	35 (24–47)	2 (0–5)	32 (23–45)	21 (11–31)
Vaccine $200												
Lower Impact	2.7 (2.1–3.2)	15.9 (11.5–20.5)	3.3 (2.5–4.1)	30.2 (21.8–38.5)	1,843.6 (1306.6–2360.0)	111 (91–131)	176 (150–202)	3 (0–8)	140 (117–163)	8 (3–14)	131 (109–154)	84 (62–108)
Moderate Impact	2.3 (1.8–2.8)	12.7 (9.1–16.3)	2.8 (2.2–3.4)	23.7 (17.0–30.9)	1382.9 (941.4–1816.2)	74 (58–91)	131 (109–153)	3 (0–6)	105 (84–124)	6 (2–12)	98 (80–118)	63 (44–83)
Higher Impact	1.6 (1.3–1.9)	6.2 (4.5–8.2)	1.7 (1.4–2.1)	11.1 (8.1–14.7)	493.5 (309.0–694.1)	37 (25–50)	43 (31–57)	1 (0–3)	34 (23–47)	2 (0–5)	32 (22–45)	21 (12–31)

Note: 95% uncertainty interval reports the results for the probabilistic sensitivity analyses. PPP = purchasing power parity. Lower impact: vaccine shortens drug treatment duration to 45 days and reduces drug dosage by 25%, the probability of adverse drug reactions by 25%, and the probability of progression by 20%; Moderate impact: vaccine shortens drug treatment duration to 30 days and reduces drug dosage by 50%, the probability of adverse drug reactions by 50%, and the probability of progression by 40%; Higher impact: vaccine shortens drug treatment duration to 15 days and reduces drug dosage by 75%, the probability of adverse drug reactions by 75%, and the probability of progression by 80%.

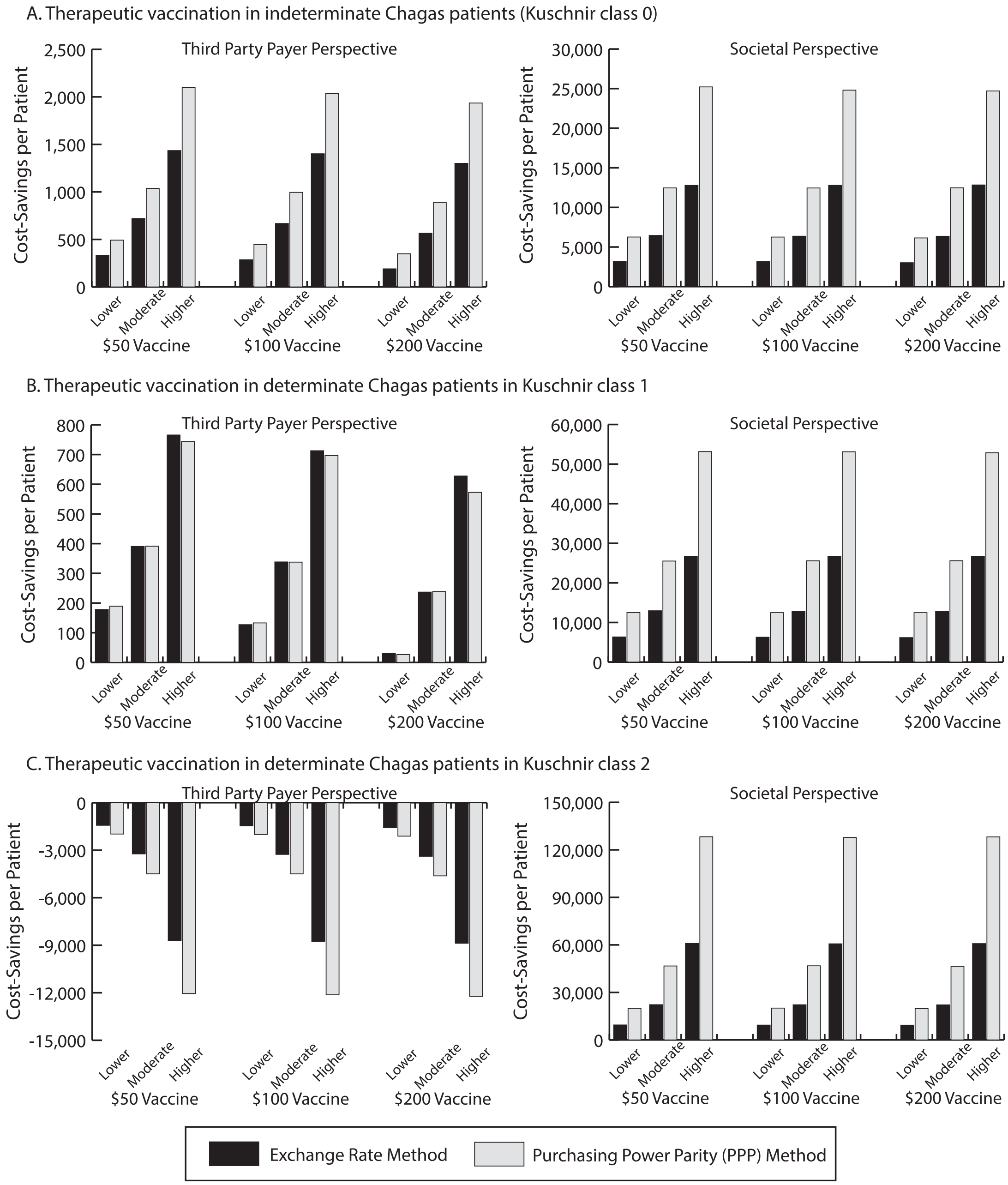

Fig. 2. Average cost-savings (2018 $US; using both conversion methods) per Chagas patient with therapeutic vaccination compared to benznidazole-only treatment in (A) indeterminate patients (Kuschnir class 0); (B) determinate patients in Kuschnir class 1; and (C) determinate patients in Kuschnir class 2. Lower impact: vaccine shortens drug treatment duration to 45 days and reduces drug dosage by 25%, the probability of adverse drug reactions by 25%, and the probability of progression by 20%; Moderate impact: vaccine shortens drug treatment duration to 30 days and reduces drug dosage by 50%, the probability of adverse drug reactions by 50%, and the probability of progression by 40%; Higher impact: vaccine shortens drug treatment duration to 15 days and reduces drug dosage by 75%, the probability of adverse drug reactions by 75%, and the probability of progression by 80%.

compared to benznidazole-only use. Vaccine-linked chemotherapy averted 18 to 280 Chagas-related deaths in Kuschnir class 2, 52 to 221 patients from progressing to Kuschnir class 3, and a total of 1049.1 to 7390.4 DALYs (varying from 20% to 80% reduction in progression risk; Table 4). Vaccination cost $1429 (lower impact, $50 vaccine, exchange rate method; $1980 PPP method) to $8874 (higher impact, $200 vaccine, exchange rate method; $12,223 PPP method) more per patient from the third-party payer perspective (Fig. 2), where the additional costs for a more effective vaccine (80% reduction in progression risk) stem from the increased lifespan and accumulation of annual medical care costs over time. However, vaccination saved ≤$60,897 per patient ($128,276 PPP method) from the societal perspective (Fig. 2).

When the vaccine reduced cardiac progression by 100%, vaccination averted 496 (95% UI: 424–551) Chagas-related deaths in Kuschnir class 2, prevented 279 patients (of 1000 treated) from progressing to Kuschnir class 3, and subsequently 198 (95% UI: 166–227) Chagas-related deaths in Kuschnir class 3, averted a total of 10,779.1 to 10,862.0 DALYs, saving ≤$89,759 and $190,049 per patient treated from the societal perspective using the exchange rate and PPP method, respectively. While the number of progression events decreased linearly with increases in progression reduction (Fig. 3a), the number of Chagas related deaths averted increased at a faster rate (Fig. 3b).

Vaccination was highly cost-effective (ICERs: $954-$1800/DALY averted) compared to benznidazole from the third-party payer per-

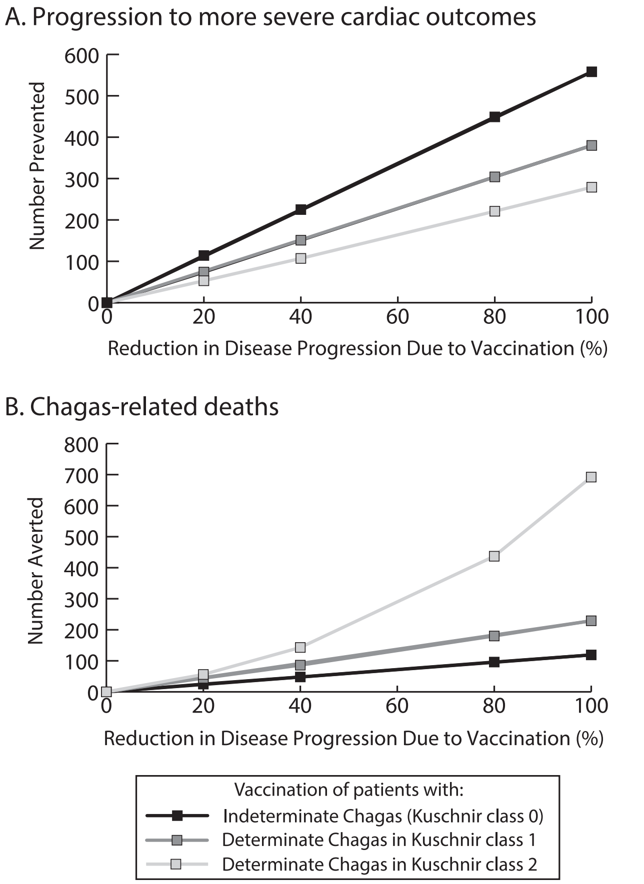

Fig. 3. Impact of therapeutic vaccination compared to benznidazole-only treatment for Chagas disease by Kuschnir class per 1000 patients treated when the vaccine reduces risk of Chagas disease progression by various amounts on (A) the total number of progressions to more severe cardiac outcomes; and (B) number of Chagas related deaths.

spective when reducing the progression of disease by ≥ 5% across all tested conditions (e.g., changes in hospital duration, bed day cost, conversion methods). From the societal perspective, vaccination was dominant compared to benznidazole when reducing the progression of disease by ≥ 5%, even up to a $200 vaccine cost, for all tested scenarios.

When reducing Chagas progression for 10 years, therapeutic vaccination was highly cost-effective from the third-party payer perspective (≤ $1403/DALY averted, exchange rate method, for vaccine costs ≤$200, probability of booster 0–50%, ≥20% reduction in outcomes) and dominant from the societal perspective. Even without a booster, therapeutic vaccination prevented ≥ 26 patients from developing more severe cardiac outcomes, ≥54 Chagas-related deaths, and 1075 DALYs of 1000 patients treated.

When the vaccine did not reduce disease progression, 37 to 112 fewer patients discontinued treatment, averting 4.5 to 31.1 DALYs per 1000 Kuschnir class 2 patients treated. Therapeutic vaccination was dominant when it resulted in a ≥ 50% reduction in drug regimen and adverse outcomes and was ≤$50 (third-party payer perspective) and when a ≥ 50% reduction in drug regimen and adverse outcomes and ≤$100 (societal perspective) and when ≥ 25% reduction in drug regimen and adverse outcomes and ≤$50 (societal perspective). Therapeutic vaccination was highly cost-effective under all other tested conditions from both perspectives ($144-$8224/DALY averted, both conversion methods), except with a 25% reduction in drug regimen and outcomes with a $200 vaccination from the third-party payer perspective, which was highly cost-effective ($9587/DALYs averted, PPP method).

4. Discussion

Our results show that therapeutic vaccination used in conjunction with benznidazole treatment for indeterminate and chronic Chagas disease not only provides health benefits but results in cost-savings (up to $89,759 or $190,049 per patient treated, depending on the conversion method used) under a wide range of scenarios for several vaccine characteristics. Thus, vaccine-linked chemotherapy may pay for itself. Even a vaccine costing $200 and 10-year duration of action, vaccination provided cost-savings and health benefits. To put this in perspective, routine dengue vaccination is estimated to cost $5865/DALY averted in Mexico from the health system perspective ($742/DALY averted from the societal perspective; in 2015 values) [30], pneumococcal vaccination in Mexico cost $4594 per quality-adjusted life year gained (in 2008 values) [31].

While, benznidazole is efficacious during the acute stage of Chagas disease [2], Chagas is often not identified this early as symptoms are typically general and short, and those infected do not seek care [32,33]. Treatment is also hindered by poor access to care, as < 1% of those infected with *T. cruzi* have access to diagnosis and treatment [34,35]. The vast majority of Chagas patients are not identified until the chronic stage of disease, when they experience cardiac symptoms [33]. Given drug treatment's poor efficacy to prevent cardiac complications and outcomes for patients with chronic Chagas disease [3], vaccination of these patients may be an ideal alternative. When given in conjunction with chemotherapy, vaccination may reduce adverse events and increase treatment completion rates, in addition to reducing the progression of cardiac complications. Preventing further disease progression is vital to prevent Chagas morbidity and mortality, as cardiac disease progression can continue even after parasites become undetectable in the bloodstream. Our results show that vaccination could prevent 9 to 279 people from further progressing and developing worse cardiac outcomes and 6 to 692 Chagas-related deaths.

As Chagas vaccines are currently under development by a consortium of institutions in Mexico and the USA, the time is right for economic evaluations as they can help guide and refine development, provide support for development, and inform plans for implementation, while there is still an opportunity to make adjustments. Once a vaccine reaches the market, there is less flexibility to make changes in design or implementation plans [12,14]. While, there is an absence of market incentive for pharmaceutical companies [1], our results provide support for continued vaccine development. Vaccine-linked chemotherapy is not only cost-effective, it actually provides cost savings compared to benznidazole-only treatment, even when only reducing the progression of disease by 5%. Our work further builds the body of evidence showing the clinical and economic benefits of vaccination for Chagas disease [11,36].

We endeavored to be conservative regarding the vaccine's impact on Chagas disease. Therefore, we did not include any costs for severe adverse events (e.g., severe dermatitis, toxic hepatitis, polyneuritis) that lead to treatment discontinuation, as they are variable and depend on treatment. Including these costs would increase the value of vaccination. We did not include the cost of stroke past the first occurrence/year, again inclusion would further increase the value of vaccination. We assumed the probability of Chagas-related death in the indeterminate state to be negligible [37,38]; however, if included, this would increase the value of a vaccine given to indeterminate patients. Additionally, we evaluated a wide range of scenarios and circumstances to determine the impact on the value of a therapeutic vaccine. For example, we varied hospitalization duration since we used Colombian data and while there are similarities between the Mexican and Colom-

Table 3
Cost (net present value, in millions $US) and number of clinical outcomes [median (95% uncertainty interval)] among 1,000 chronic Chagas patients in Kuschnir class 1 treated with benznidazole and vaccine-linked chemotherapy with a lifetime duration of reducing risk of progression.

	Cost Third-Party Payer Perspective (Exchange Rate Method)	Cost Societal Perspective (Exchange Rate Method)	Cost Third-Party Payer Perspective (PPP Method)	Cost Societal Perspective (PPP Method)	Disability-Adjusted Life Years (DALYs)	Discontinue Treatment	Chagas Related Death in Kuschnir Class 1	Progress to Kuschnir Class 2	Chagas Related Death in Kuschnir Class 2	Progress to Kuschnir Class 3	Chagas Related Death in Kuschnir Class 3
Drug Treatment Only											
Benznidazole	8.9 (7.5–10.1)	47.1 (37.6–55.2)	13.6 (11.4–15.6)	90.5 (72.4–107.8)	10,024.4 (8267.4–11,497.1)	148 (126–171)	85 (61–113)	196 (173–220)	12 (6–19)	184 (162–209)	132 (108–156)
Drug Treatment plus Vaccination											
Vaccine $50											
Lower Impact	8.7 (7.3–9.9)	40.8 (32.8–48.1)	13.4 (11.0–15.5)	78.0 (63.0–93.8)	9408.0 (7821.0–10,733.6)	112 (94–133)	71 (51–96)	158 (135–180)	9 (4–16)	148 (126–170)	105 (83–125)
Moderate Impact	8.5 (7.1–9.7)	34.0 (27.4–40.3)	13.3 (11.0–15.2)	65.1 (51.6–78.0)	8872.2 (7347.6–10,166.2)	74 (58–91)	57 (39–78)	118 (99–139)	7 (3–13)	111 (92–132)	79 (61–97)
Higher Impact	8.1 (6.7–9.4)	20.3 (16.4–24.0)	12.9 (10.6–15.0)	37.5 (29.9–45.4)	7616.2 (6282.1–8738.0)	37 (26–49)	21 (12–31)	39 (28–54)	2 (0–6)	37 (25–50)	26 (17–38)
Vaccine $100											
Lower Impact	8.7 (7.3–10.0)	40.7 (32.3–48.3)	13.5 (11.2–15.4)	78.6 (62.8–92.5)	9392.1 (7799.9–10,714.8)	111 (93–130)	71 (49–94)	159 (135–180)	9 (4–16)	149 (126–169)	106 (85–126)
Moderate Impact	8.6 (7.1–9.7)	34.2 (27.6–40.7)	13.3 (11.1–15.3)	65.2 (51.5–77.3)	8907.0 (7337.3–10,076.0)	74 (59–90)	56 (39–77)	118 (99–139)	7 (3–13)	111 (92–131)	79 (62–99)
Higher Impact	8.2 (6.7–9.4)	20.5 (16.3–24.3)	12.9 (10.7–14.9)	37.5 (30.1–45.1)	7600.9 (6326.1–8702.1)	37 (25–50)	21 (12–32)	39 (28–52)	2 (0–6)	37 (26–49)	26 (17–37)
Vaccine $200											
Lower Impact	8.8 (7.4–10.0)	40.8 (32.6–48.3)	13.7 (11.4–15.6)	78.6 (63.8–92.3)	9400.6 (7834.7–10,794.6)	111 (93–131)	71 (50–96)	157 (134–181)	9 (4–16)	147 (126–171)	105 (85–127)
Moderate Impact	8.6 (7.2–9.9)	34.3 (27.2–40.5)	13.5 (11.0–15.4)	65.1 (52.1–78.3)	8811.4 (7277.2–10,144.6)	74 (57–91)	56 (39–77)	118 (99–137)	7 (3–13)	111 (93–130)	79 (62–97)
Higher Impact	8.2 (6.8–9.5)	20.5 (16.3–24.3)	13.0 (10.7–15.1)	38.0 (29.9–45.2)	7584.3 (6329.4–8708.3)	37 (26–50)	20 (12–32)	40 (28–52)	2 (0–6)	37 (26–49)	26 (16–37)

Note: 95% uncertainty interval reports the results for the probabilistic sensitivity analyses. PPP = purchasing power parity. Lower impact: vaccine shortens drug treatment duration to 45 days and reduces drug dosage by 25%, the probability of adverse drug reactions by 25%, and the probability of progression by 20%; Moderate impact: vaccine shortens drug treatment duration to 30 days and reduces drug dosage by 50%, the probability of adverse drug reactions by 50%, and the probability of progression by 40%; Higher impact: vaccine shortens drug treatment duration to 15 days and reduces drug dosage by 75%, the probability of adverse drug reactions by 75%, and the probability of progression by 80%.

bian healthcare systems (e.g., have universal coverage [39], ≥92% of population covered [40] and similar average hospital durations [41]), hospitalization may differ in Mexico. While our model focuses on the individual perspective, including the full population impact to estimate the complete public health value [42] would further increase the value of therapeutic vaccination.

4.1. Limitations

All models are simplifications of real life and as such cannot represent every Chagas event or outcome. Our model drew from literature of varying quality, and results may change as better data becomes available. For example, data describing the progression of cardiac outcomes in Chagas patients over time is lacking. Our model is calibrated to the best data available, anecdotal evidence, and follows clinical expert option but, our results may change with more details on disease progression over a Chagas patient's lifetime. We excluded the probability and cost associated with heart transplantation, as they are rarely performed in Mexico. We also did not consider specific annual treatments and costs that may be incurred. While not evaluated in the current study, pregnant women represent another potential target group for vaccination, as chemotherapy for Chagas is contraindicated in pregnancy [4].

4.2. Conclusions

Therapeutic vaccination used in conjunction with benznidazole treatment for indeterminate and chronic Chagas disease would reduce the number of patients experiencing worse cardiac outcomes and provide cost-savings under a wide range of conditions, regardless of the impact of vaccination on reducing clinical progression of disease.

Funding

This work was supported by the Carlos Slim Foundation, Mexico Agency for Healthcare Research and Quality (AHRQ) via grant R01HS023317, the National Institute of General Medical Sciences (NIGMS) via MIDAS grant U24GM110707, and the United States Agency for International Development (USAID) under agreement

Table 4
Cost (net present value, in millions $US) and number of clinical outcomes [median (95% uncertainty interval)] among 1,000 chronic Chagas patients in Kuschnir class 2 treated with benznidazole and vaccine-linked chemotherapy with a lifetime duration of reducing risk of progression.

	Cost Third-Party Payer Perspective (Exchange Rate Method)	Cost Societal Perspective (Exchange Rate Method)	Cost Third-Party Payer Perspective (PPP Method)	Cost Societal Perspective (PPP Method)	Disability-Adjusted Life Years (DALYs)	Discontinue Treatment	Chagas Related Death in Kuschnir Class 2	Progress to Kuschnir Class 3	Chagas Related Death in Kuschnir Class 3
Drug Treatment Only									
Benznidazole	15.1 (13.4–16.6)	124.0 (103.2–141.6)	21.0 (18.5–23.2)	241.8 (196.9–275.2)	15,125.8 (12,599.8–17,283.9)	148 (126–172)	493 (429–549)	279 (252–309)	199 (167–231)
Drug Treatment plus Vaccination									
Vaccine $50									
Lower Impact	16.5 (14.5–18.3)	113.9 (94.3–131.0)	23.1 (20.2–25.5)	221.9 (179.6–254.7)	14,076.7 (11,581.9–16,043.5)	111 (93–131)	475 (405–536)	227 (202–252)	161 (134–191)
Moderate Impact	18.3 (16.1–20.4)	101.8 (82.5–117.1)	25.6 (22.0–28.3)	194.7 (155.4–224.6)	12,438.7 (10,193.4–14,340.4)	74 (58–90)	427 (357–493)	172 (149–196)	122 (98–147)
Higher Impact	23.8 (20.2–26.9)	63.0 (50.5–73.4)	33.1 (27.5–37.6)	112.5 (89.8–132.9)	7816.4 (6438.3–9090.5)	37 (26–49)	213 (168–263)	58 (44–74)	42 (30–56)
Vaccine $100									
Lower Impact	16.6 (14.5–18.2)	115.1 (94.1–131.4)	23.1 (20.2–25.5)	220.4 (181.3–253.5)	14,027.9 (11,482.3–15,961.3)	111 (92–130)	474 (400–532)	226 (200–251)	162 (133–186)
Moderate Impact	18.4 (15.8–20.3)	102.5 (83.7–117.4)	25.5 (22.1–28.2)	194.0 (157.5–225.8)	12,408.1 (10,278.4–14,336.8)	74 (59–90)	427 (358–495)	172 (148–195)	122 (98–145)
Higher Impact	23.9 (20.0–27.2)	63.0 (50.2–74.4)	33.2 (27.7–37.8)	111.2 (89.1–131.5)	7835.4 (6377.7–9172.8)	37 (25–49)	215 (168–265)	59 (44–74)	42 (29–56)
Vaccine $200									
Lower Impact	16.7 (14.7–18.3)	114.8 (94.1–131.0)	23.2 (20.2–25.5)	221.2 (180.3–253.6)	14,044.4 (11,685.6–16,019.1)	111 (92–132)	475 (410–536)	226 (201–252)	161 (135–188)
Moderate Impact	18.6 (16.1–20.5)	102.2 (82.6–117.7)	25.7 (22.2–28.6)	194.2 (156.5–224.6)	12,496.7 (10,222.2–14,439.2)	73 (57–90)	431 (360–496)	172 (148–193)	122 (98–144)
Higher Impact	24.1 (20.1–27.2)	63.4 (50.5–74.5)	33.3 (27.7–37.9)	112.0 (88.2–133.2)	7855.6 (6378.6–9122.5)	38 (26–50)	215 (168–262)	58 (44–73)	42 (29–56)

Note: 95% uncertainty interval reports the results for the probabilistic sensitivity analyses. PPP = purchasing power parity. Lower impact: vaccine shortens drug treatment duration to 45 days and reduces drug dosage by 25%, the probability of adverse drug reactions by 25%, and the probability of progression by 20%; Moderate impact: vaccine shortens drug treatment duration to 30 days and reduces drug dosage by 50%, the probability of adverse drug reactions by 50%, and the probability of progression by 40%; Higher impact: vaccine shortens drug treatment duration to 15 days and reduces drug dosage by 75%, the probability of adverse drug reactions by 75%, and the probability of progression by 80%.

number AID-OAA-A-15-00064. The funders had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; and preparation, review, or approval of the manuscript.

Declaration of Competing Interest

SMB, LA, US, SM, SR, and BYL have no significant conflicts of interest.

JAFL works for the Carlos Slim Foundation but has no competing financial interests.

MEB and PJH are patentholders and lead investigators of a program for the development of a therapeutic Chagas disease vaccine.

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