The Potential Economic Value of a Therapeutic Chagas Disease Vaccine for Pregnant Women to Prevent Congenital Transmission

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Declaration of interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Abstract

Background: Currently, there are no solutions to prevent congenital transmission of Chagas disease during pregnancy, which affects 1–40% of pregnant women in Latin America and is associated with a 5% transmission risk. With therapeutic vaccines under development, now is the right time to determine the economic value of such a vaccine to prevent congenital transmission.

Methods: We developed a computational decision model that represented the clinical outcomes and diagnostic testing strategies for an infant born to a Chagas-positive woman in Mexico and evaluated the impact of vaccination.

Results: Compared to no vaccination, a 25% efficacious vaccine averted 125 [95% uncertainty interval (UI): 122–128] congenital cases, 1.9 (95% UI: 1.6–2.2) infant deaths, and 78 (95% UI: 66–91) DALYs per 10,000 infected pregnant women; a 50% efficacious vaccine averted 251 (95% UI: 248–254) cases, 3.8 (95% UI: 3.6–4.2) deaths, and 160 (95% UI: 148–171) DALYs; and a 75% efficacious vaccine averted 376 (95% UI: 374–378) cases, 5.8 (95% UI: 5.5–6.1) deaths, and 238 (95% UI: 227–249) DALYs. A 25% efficacious vaccine was cost-effective (incremental cost-effectiveness ratio <3x Mexico's gross domestic product per capita, <$29,698/DALY averted) when the vaccine cost $240 and $310 and cost-saving when $10 and $80 from the third-party payer and societal perspectives, respectively. A 50% efficacious vaccine was cost-effective when costing $490 and $615 and cost-saving when $25 and $160, from the third-party payer and societal perspectives, respectively. A 75% efficacious vaccine was cost-effective when $720 and $930 and cost-saving when $40 and $250 from the third-party payer and societal perspectives, respectively. Additionally, 13–42 fewer infants progressed to chronic disease, saving $0.41-$1.21 million to society.

Conclusion: We delineated the thresholds at which therapeutic vaccination of Chagas-positive pregnant women would be cost-effective and cost-saving, providing economic guidance for decision-makers to consider when developing and bringing such a vaccine to market.

Keywords

Introduction

The prevalence of Chagas disease among pregnant women in Latin America is 1–40%[1–6], however, with no current solutions for preventing congenital transmission (5% risk[7]) once pregnant, pregnant women may be an ideal target population for vaccination. With vaccines currently under development, now is the time to determine the economic value of a therapeutic Chagas disease vaccine for pregnant women to prevent congenital transmission. While the majority of congenital infections are asymptomatic, *Trypanosoma cruzi*-infected infants can develop moderate to severe symptoms (e.g., respiratory distress syndrome after preterm birth, splenomegaly, hepatomegaly, and cardiomyopathy), with up to 6.5% of cases resulting in death.[1] Chagas disease is often difficult to diagnose even among symptomatic infants, as many other congenital infections have similar symptoms (e.g., TORCH: toxoplasmosis, other infections, rubella, cytomegalovirus, herpes simplex).[8] Diagnosis in infants is further complicated by requiring multiple diagnostic tests over the

course of a year,[8] leading many Chagas-positive infants to be lost to follow-up and remain untreated.[9, 10] Additionally, congenitally-infected infants are thought to grow up with the same 20–30% chance of developing chronic disease that would occur if vectorially infected. [3]

As treatment is contraindicated in pregnancy[9, 11, 12], vaccination may be a viable option for preventing congenital transmission. As at least 12 vaccine candidates are in pre-clinical trials,[13] 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. With vaccines in the pipeline, evaluating the economic value prior to licensure can help guide development and implementation, desired efficacy profiles, and vaccine price points while there is still time to make adjustments.[14–16] Therefore, a computational simulation model was developed to evaluate the clinical and economic impact of a therapeutic vaccine given to pregnant women to prevent congenital Chagas infections in Mexico. Mexico served as a test case as it has one of the highest number of persons living with Chagas disease[17, 18] and a high number of congenital Chagas disease cases.[7, 19]

Methods

Model

Using TreeAge Pro 2019 (Williamstown, MA), we developed a computational decision analytic model to represent the clinical outcomes and diagnostic testing strategies for an infant born to a Chagas-positive woman in Mexico and evaluated the impact of therapeutic vaccination from the third-party payer and societal perspectives. Figure 1 outlines the model structure. A Chagas-positive pregnant woman entered the model and could transmit the parasite to the fetus in utero at any point during the pregnancy or at birth based on the probability of transmission.[20, 21] Each woman in the model could either be vaccinated or not vaccinated. Vaccination, assumed to be administered during the first trimester, attenuated the probability of congenital transmission by its efficacy and had a probability of minor side effects.[22] We assumed vaccination efficacy and cost was for a full vaccination series, and that each woman was fully compliant with vaccination prior to giving birth.

Infected infants had a probability of being symptomatic or asymptomatic. Symptomatic infants had a probability of Chagas-attributable mortality within 24 hours after birth. Those that survived, had a probability of Chagas-related preterm birth (<37 weeks gestation), with those preterm infants having an associated probability of mortality due to complications, varying with gestational age. Preterm infants stayed in the neonatal intensive care unit (NICU), with the duration based on their gestational age and mortality risk. Symptomatic full-term infants had a probability of moderate symptoms (e.g., hepatomegaly, splenomegaly, hepatosplenomegaly, anemia, petechiae, anasarca) or severe symptoms (e.g., respiratory distress syndrome, meningoencephalitis, and cardiomyopathy). All full-term infants with symptoms stayed in the NICU for the duration of their symptoms.

Care of infants born to Chagas-positive women followed recommendations by Carlier et al. [8] As all women were Chagas-positive in our model, all infants underwent a micromethod diagnostic test (i.e., direct parasitological detection by microscopic examination) at birth.

Infants were deemed Chagas-positive based on the test's associated sensitivity and specificity and if the infant was infected with *T. cruzi*. Those testing positive received treatment with benznidazole, regardless of their true infection status (i.e., true and false positives). Those testing negative had a follow-up clinic visit at 8 months of age (i.e., after maternal antibodies had disappeared) to perform serological testing, for which infants had a probability of returning for this testing. The serological testing consisted of an algorithm of 2 tests, an indirect hemagglutination assay (IHA) and an enzyme-linked immunosorbent assay (ELISA based IgG serology) test. Infants were deemed Chagas-positive based on the test sensitivity and specificity and if they were infected with *T. cruzi*. Again, those testing positive were treated with benznidazole, while a negative IgG serology result confirmed that the infant did not have Chagas.

Benznidazole treatment (5mg/kg/day for 60 days) was based on current recommendations[23, 24] and was associated with probabilities of minor side effects (e.g., allergic reaction), treatment completion (i.e., >80% of regimen), and being curative. As benznidazole is well tolerated and highly effective in children <1-year-old[9, 12, 25], only minor side effects were considered, which was associated with the cost of treatment (i.e., antihistamines).

For each simulation, the incremental cost-effectiveness ratio (ICER) was calculated as:

$$\text{ICER} = (\text{Cost}_{\text{Vaccine}} - \text{Cost}_{\text{No Vaccine}})/(\text{Health Effects}_{\text{No Vaccine}} - \text{Health Effects}_{\text{Vaccine}})$$

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 ICER represents the difference in costs and effectiveness between vaccination and no vaccination. As DALYs measure years of perfect health lost (where 0 is perfect health and 1 is death), the ICER calculates the cost per DALY averted, thus uses a denominator in which no vaccination is first.[26]

The third-party payer or health system perspective included all direct medical costs of services and treatment (e.g., hospitalization, diagnostics, treatment), while the societal perspective included direct and indirect (e.g., productivity losses due to absenteeism and mortality) costs. The cost per NICU bed day and duration of the NICU stay were used to estimate NICU hospitalization costs. Daily wage served as a proxy for productivity losses associated with absenteeism and mortality (e.g., human capital approach).[27] A Chagas-specific premature death resulted in accruing the net present value (NPV) of that infant's lifetime earnings, based on their life expectancy.[28] We assumed all infants with Chagas accrued productivity losses, as everyone is assumed to contribute to society. All costs are

in 2019 $US, with all 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 ICERs were <$9,989 (Mexico's gross domestic product, GDP, per capita[29]) per DALY averted; cost-effective if 1–3 times the GDP, and not cost-effective if >3 times the GDP.

Data Sources

Table 1 shows the model input parameters, values, and sources. All data were extracted from scientific literature or international databases and were age-specific and Mexico-specific when available. When converting costs between currencies, costs were discounted and then converted into US dollars using an exchange rate of 19.2 which was the average for 2019 as of August 1, 2019.[30] Life expectancy came from the World Health Organization (WHO) Global Health Observatory based on the current birth cohort in Mexico.[28] Daily income came from the reported national quarterly income, which includes other benefits (e.g., pensions, fringe benefits).[27] The risk of congenital transmission came from a systematic review and meta-analysis[7] and used the pooled risk of congenital transmission in endemic countries as the current estimate for this risk (modeled as a distribution with a median of 5%, range: 4% to 6%; Table 1). NICU bed day, clinic visits, and diagnostic tests costs came from Mexico-specific literature and national sources such as the Mexican Social Security Insititute.[31] Disability-weights came from the 2017 Global Burden of Disease.[32] Due to the lack of specific disability weights related to congenital Chagas, the model assumed that acute encephalitis served as a proxy for severe symptoms in infants and moderate anemia due to neglected tropical disease served as a proxy for moderate symptoms.

Experiments and Sensitivity Analyses

Each simulation sent a Chagas-positive pregnant woman through the model 2,000 times. Each time she traveled through the model, Monte Carlo simulations (i.e., probabilistic sensitivity analyses) consisting of 2,000 trials simultaneously varied each parameter throughout their ranges (based on data availability and reported variability) in Table 1 (for a total of 4 million trials with unique outcomes). Multiway sensitivity analyses simultaneously varied vaccination cost ($10-$900) and vaccine efficacy (25%−75%) to help identify thresholds at which the economic value of vaccination would change. Vaccination cost was assumed to include the price of the vaccine itself, vaccine administration, and any other health systems costs. Additional multiway sensitivity analyses varied the congenital transmission risk (from 0.1% to 18%[7, 12]) to account for previous treatment and explore the extremes reported in the literature. We also estimated the lifetime costs of those infants that could progress to chronic disease by multiplying the number of cases that could progress by the lifetime cost per chronic Chagas disease case (Table 1), assuming 20–30% would progress to chronic Chagas disease[34, 35].

Results

Clinical and Economic Impact of Therapeutic Vaccination with the Current Transmission Risk Estimate

Table 2 shows the clinical (e.g., number of congenital cases and deaths) and economic (e.g., cost, DALYs) outcomes of Chagas vaccination per 10,000 infected pregnant women based on current estimates for the risk of congenital transmission (distribution with a median of 5%, range 4%–6%). Compared to no vaccination, a 25% efficacious therapeutic vaccination averted 125 (95% UI: 122–128) congenital cases, 1.9 (95% UI: 1.6–2.2) infant deaths, and 78 (95% UI: 66–91) DALYs per 10,000 infected pregnant women; a 50% efficacious vaccine averted 251 (95% UI: 248–254) congenital cases, 3.8 (95% UI: 3.6–4.2) infant deaths, and 160 (95% UI: 148–171) DALYs; and a 75% efficacious vaccine averted 376 (95% UI: 374–378) congenital cases, 5.8 (95% UI: 5.5–6.1) infant deaths, and 238 (95% UI: 227–249) DALYs. Vaccination also reduced the number of infants that can progress to chronic disease due to missing treatment opportunities (i.e., false-negative or lost to follow up) or those that did not successfully complete treatment (i.e., not cured or discontinued). Table 3 shows the number of these infants that progress to chronic disease and the resulting lifetime costs. Vaccination prevented 13–42 infants from later developing chronic Chagas disease, saving $42,487 (95% UI: $39,965-$45,103) to $131,452 (95% UI: $129,242-$133,661)6 from the third-party payer perspective and $403,083 (95% UI: $373,172-$432,995) to $1.22 million (95% UI: $1.19-$1.24 million) from the societal perspective, over the course of their lifetimes (Table 3).

Figure 2 shows how the s varies with vaccination cost and vaccine efficacy from both perspectives and outlines cost-effectiveness thresholds. For example, from the third-party payer perspective, vaccination with a 25% efficacious vaccine was cost-effective when $240 ($29,023/DALY averted), highly cost-effective when $85 ($9,267/DALY averted), and economically dominant (i.e., saved costs and provided health benefits) when $10 (saving $4 per vaccinee) compared to no vaccination. A 75% efficacious vaccine was cost-effective up to $720 ($29,837/DALY averted) and up to $930 ($29,509/DALY averted) from the third-party payer and societal perspectives, respectively. From the societal perspective, a 25% efficacious vaccine was economically dominant when costing $80 (saving $44 per vaccinee); a 50% efficacious vaccine was dominant when costing $160 (saving $0.50 per vaccinee); and a 75% efficacious vaccine was dominant costing $250 (saving $48 per vaccinee). Figure 4 shows the probability that vaccination is cost-effective compared to no vaccination at various willingness-to-pay thresholds. For example, a 50% efficacious vaccine costing $200 was cost-effective in 58% of simulations and 65% of simulations at a willingness-to-pay threshold of $12,000/DALY averted from the third-party payer and societal perspectives, respectively.

Clinical and Economic Impact of Therapeutic Vaccination when Varying Transmission Risk

Figure 3 shows how the ICER varies with the risk of congenital transmission (from 0.1% to 18%) and vaccine efficacy. With lower risks for congenital transmission, the change in ICERs had a steeper slope than higher risks of transmission (Figure 3). Vaccination was cost-effective for risks 0.4% ($25,497/DALY averted) from the third-party payer

perspective and for risks 0.3% ($24,196/DALY averted) from the societal perspective when 75% efficacious and costing $50. Vaccination was dominant (saving $3 per vaccinee) when then transmission risk was 1.1% and the vaccination cost $50 and was 75% efficacious from the societal perspective (Figure 3b). While a $200 vaccination was dominant when the risk was 4% and the vaccine was 75% efficacious. A 25% efficacious, $50 vaccine was highly cost-effective when the risk of transmission was 3% and dominant when 18% (third-party payer perspective).

Discussion

This study defines circumstances and vaccine characteristics thresholds where a therapeutic Chagas disease vaccine for pregnant women to prevent congenital transmission would be cost-effective, highly cost-effective, and cost saving. Vaccination can avert up to 375 congenital cases and 5 infant deaths per 10,000 Chagas-infected pregnant women. This vaccine does not need to have highly favorable characteristics (e.g., 75% efficacy) in order to be beneficial. Vaccination can cost as high as $900 and still be cost-effective under certain conditions. Of course, this cost includes the vaccine, administration, supply chain and logistics, and service delivery costs, but a large percentage of this cost may be the price of the vaccine. The price of the vaccine can be a challenging issue. Showing that a higher vaccine price can be supported may encourage more manufacturers to develop and produce Chagas disease vaccines. However, the vaccine also needs to be affordable to be of broader use.

These results show that even a 25% efficacious vaccine could be cost-effective, suggesting that even with a lower efficacy, it still would have value. Expecting all vaccines to have efficacies above 50% is unrealistic and discounts the value that vaccines with lower efficacy may provide. If a candidate vaccine proves in preclinical/clinical trials to have a low efficacy, it does not mean this candidate should be disregarded as some vaccines have low to modest efficacies (e.g., the influenza[36], Bacille Calmette-Guerin (BCG)[37, 38], and RTS, S[39–42] vaccines). Thus, if the Chagas disease vaccine candidate proves to have an efficacy below 50%, it should not necessarily be a reason to discontinue development or prevent use.

Pregnant women represent an ideal target population for vaccination as once Chagas-positive and pregnant, it is too late to potentially prevent congenital transmission given current drug treatments (e.g., benznidazole and nifurtimox) are contraindicated in pregnancy[9, 11, 12]. This may be the case in many situations as many Chagas-infected individuals do not know they are infected, and many remain unidentified until experiencing symptoms associated with chronic disease. In this setting, the therapeutic vaccine would be a stand-alone antenatal intervention. However, the possibility remains that it might also find use in a vaccine-linked chemotherapy strategy, in which an antiparasitic drug is co-administered with the therapeutic vaccine. Potentially this approach could reduce the dose required for drug treatment, possibly increasing the safety profile of current antiparasitic drugs for use in pregnancy. Still another possible target population for vaccination is women prior to pregnancy (i.e., preconception).[43] This is based on the success of treating this population, wherein several studies have found that treating women prior to pregnancy will prevent congenital infection.[11, 12, 44, 45]

In each of these settings, both women's health and antenatal care clinics present important opportunities to vaccinate those that are infected with *T. cruzi*. Thus, serving as a primary prevention strategy for infants and a complementary intervention to existing antiparasitic treatment and prevention.[43] An overall goal of linking a therapeutic Chagas disease vaccine to reproductive health would be to eliminate congenital Chagas disease. Even as vector control initiatives continue to be effective, congenital infections accounted for approximately 22% of all infections in 2010.[46]

The vaccine's proposed mechanism of action would include both reducing the maternal parasite burden in target organs (including the heart, thereby reducing cardiac fibrosis) and possibly parasitemia, which is a key factor associated with congenital transmission. In fact, even if the risk of transmission was 0.3% (under the 5% currently estimated[7]), a vaccine would still be cost-effective. While observational studies suggest that in women previously treated with benznidazole the congenital transmission risk is 0%[11, 44, 45], randomized controlled trials have not been performed. Thus, a modest risk of transmission (e.g., lower than 5%) may be possible, thus, potentially leaving room for additional reduction in transmission by a vaccine.

However, economics is not the only thing to consider when determining if a vaccine is appropriate for pregnant women, as there are additional challenges, such as the type of vaccine, timing of immunization, and how to implement immunization. Live vaccines are not safe to administer during pregnancy[47]; yet, other vaccine formulations (killed or inactivated) serve as the basis for several routine vaccines given to pregnant women, such as influenza; tetanus, diphtheria, and pertussis (Tdap); hepatitis B; and polio.[48] Other considerations include the education of mothers and providers, healthcare services utilization, communications, and long-term surveillance and assessment of vaccine safety.[49] Developers and decision makers need to understand these key challenges for development and implementation, as well as thresholds of vaccination cost and efficacy that make this vaccine cost-effective. This study further builds the body of evidence showing the clinical and economic benefits of vaccination for Chagas disease.[50–52]

To be conservative, we did not include long-term outcomes of Chagas disease in infected, untreated children in the ICER calculations, as this would have increased the value of vaccination. However, we did estimate the costs these children could incur and the potential savings due to vaccination. The model did not include specific care for infants with mild symptoms as treatment is non-specific and it is often unknown that they are Chagas-positive. We also did not include any potential benefits of vaccination to the mother. For example, previous work has shown that therapeutic vaccination to reduce the progression of Chagas disease for patients with indeterminate disease and those with early cardiac symptoms is highly cost-effective and provides cost savings.[52] Including these would further increase the value of vaccination for a pregnant woman.

Limitations

All models are simplifications of real-life and therefore cannot account for every Chagas event or outcome. Current literature on congenital Chagas disease is limited and therefore, the model drew from data of varying quality, thus these results can be refined as new and

better data become available. Additionally, the model did not distinguish between different treatments within Chagas symptom categories (moderate and severe) because the included symptoms are treated based on the underlying cause. The model did not include severe vaccine side effects as they are uncommon in currently existing vaccines.[53] We included only costs incurred during the NICU stay and those related to Chagas-diagnosis and treatment post-discharge. Therefore, we did not consider homecare costs such as pharmacy visits. We also did not include costs parents/caregivers may incur such as co-payments for treatment (which would vary based on insurance), transportation, food, lodging, or additional productivity losses which they may incur.

Conclusion

This study outline thresholds where therapeutic Chagas vaccination for an infected pregnant woman to prevent congenital transmission would be cost-effective, highly cost-effective, and cost saving for decision-makers such as developers, manufacturers, funders, and policy makers to consider when developing and implementing a therapeutic Chagas vaccine.

Acknowledgments

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Figure 1.
Model outline.

A. Third-party payer perspective

B. Societal perspective
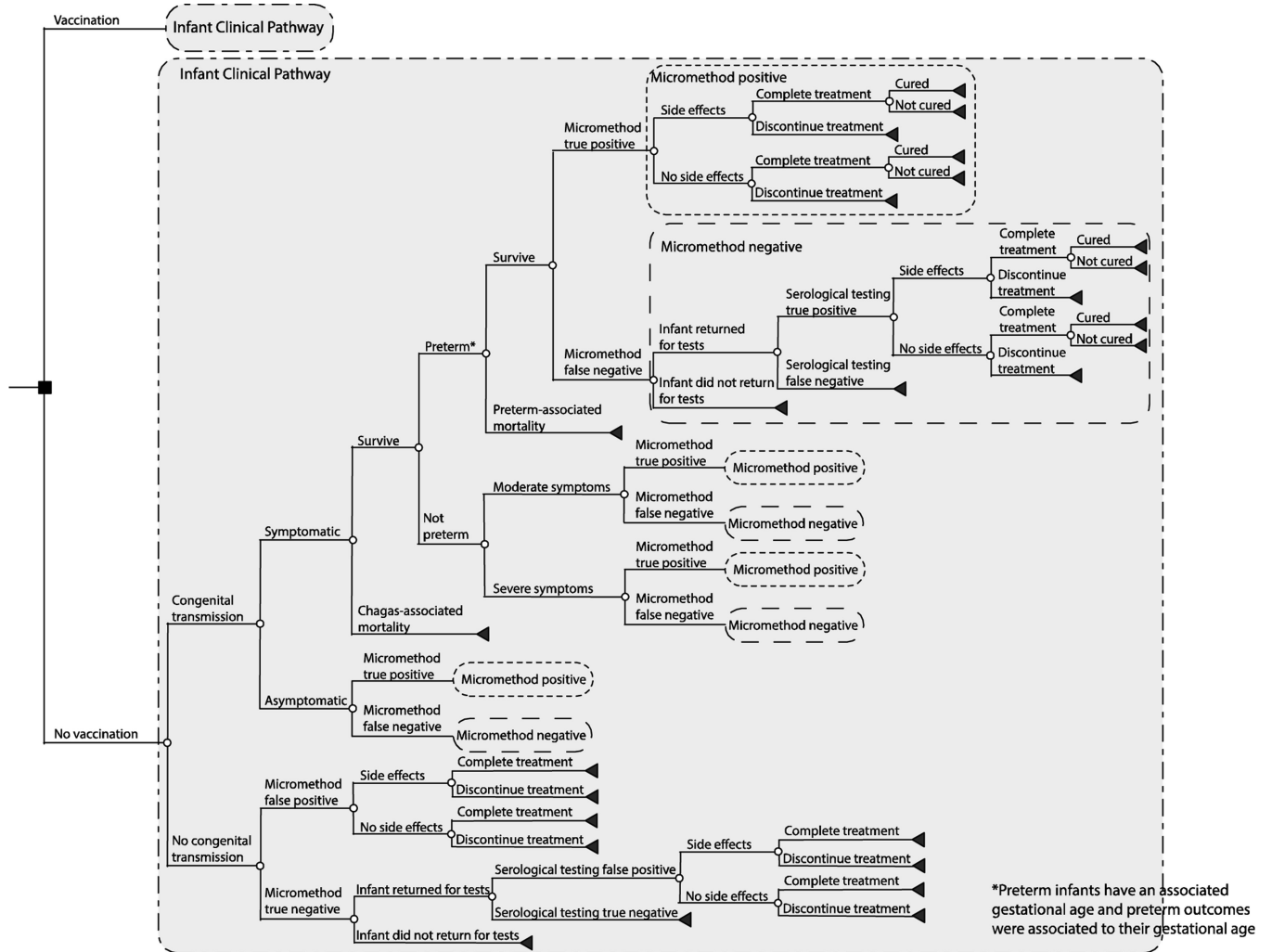
Vaccine efficacy: —— 25% – – 50% - - - - 75%
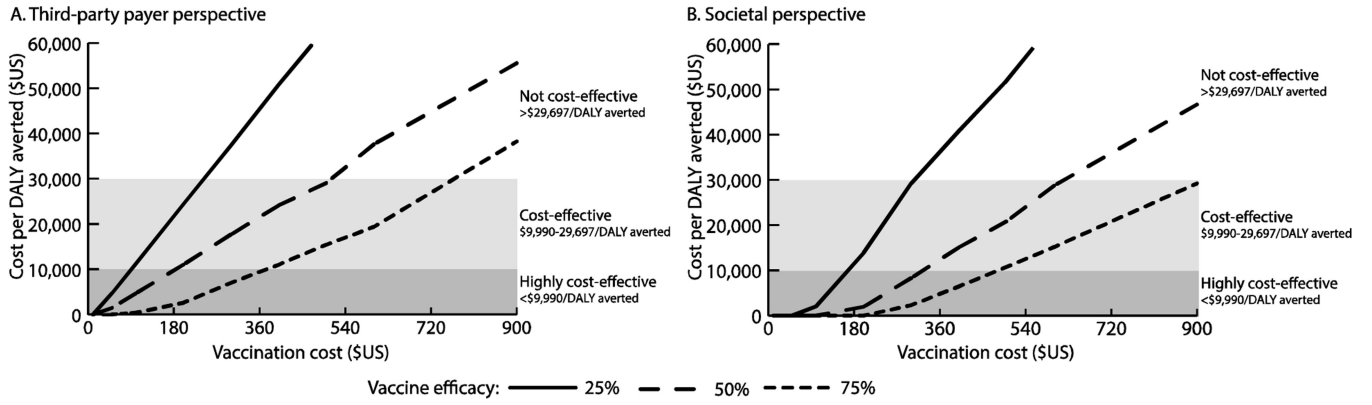
Figure 2.

Impact of varying vaccination cost and vaccine efficacy on the incremental cost-effectiveness ratio (ICER) of a therapeutic vaccine given to pregnant women to prevent congenital transmission with current transmission estimates (distribution with a median of 5%, range: 4%–6%) from (A) the third-party payer perspective, and (B) the societal perspective. An ICER of 0 indicates that the vaccination strategy would be economically dominant (i.e., provides cost savings and positive health benefits); ICERs >$60,000/ disability-adjusted life year (DALY) averted are not shown.

A. $50 vaccination from the third-party payer perspective

B. $50 vaccination from the societal perspective

C. $200 vaccination from the third-party payer perspective

D. $200 vaccination from the societal perspective

Vaccine efficacy: —— 25% — — 50% - - - - 75%
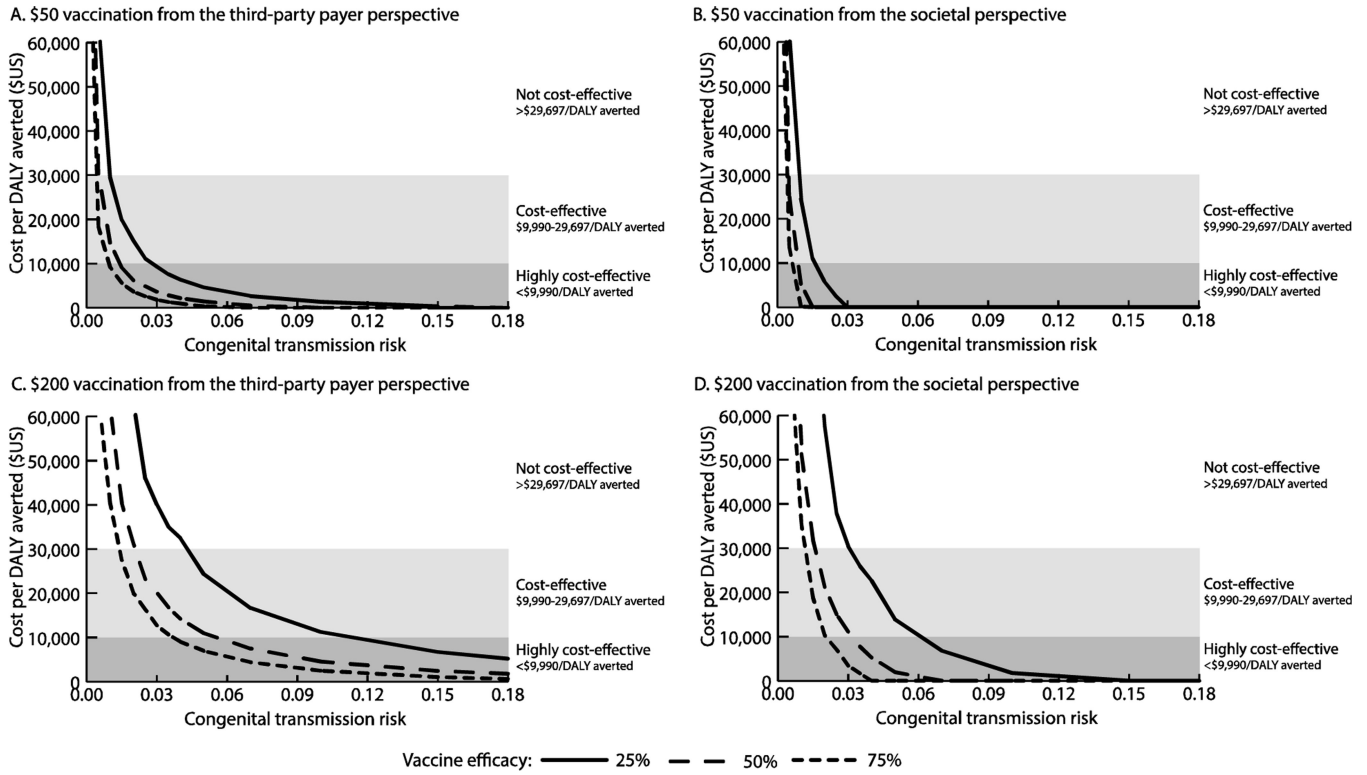
Figure 3.
Impact of varying vaccine efficacy and congenital transmission risk on the incremental cost-effectiveness ratio (ICER) of a therapeutic vaccine given to pregnant women to prevent congenital transmission with (A) $50 vaccination from the third-party payer perspective, (B) $50 vaccination from the societal perspective, (C) $200 from the third-party payer perspective, and (D) $200 from the societal perspective. An ICER of 0 indicates that the vaccination strategy would be economically dominant (i.e., provides cost savings and positive health benefits); ICERs >$60,000/disability-adjusted life year (DALY) averted are not shown.

A) Third-party payer perspective

B) Societal perspective

Vaccination cost: ——— $50 ——— $200 ——— $500

Figure 4.
Percent of simulation trials in which vaccination was cost-effective compared to no vaccination over a range of willingness-to-pay thresholds from the (A) third-party payer perspective and (B) societal perspective.

Table 1.

Model input parameters, values, and sources.

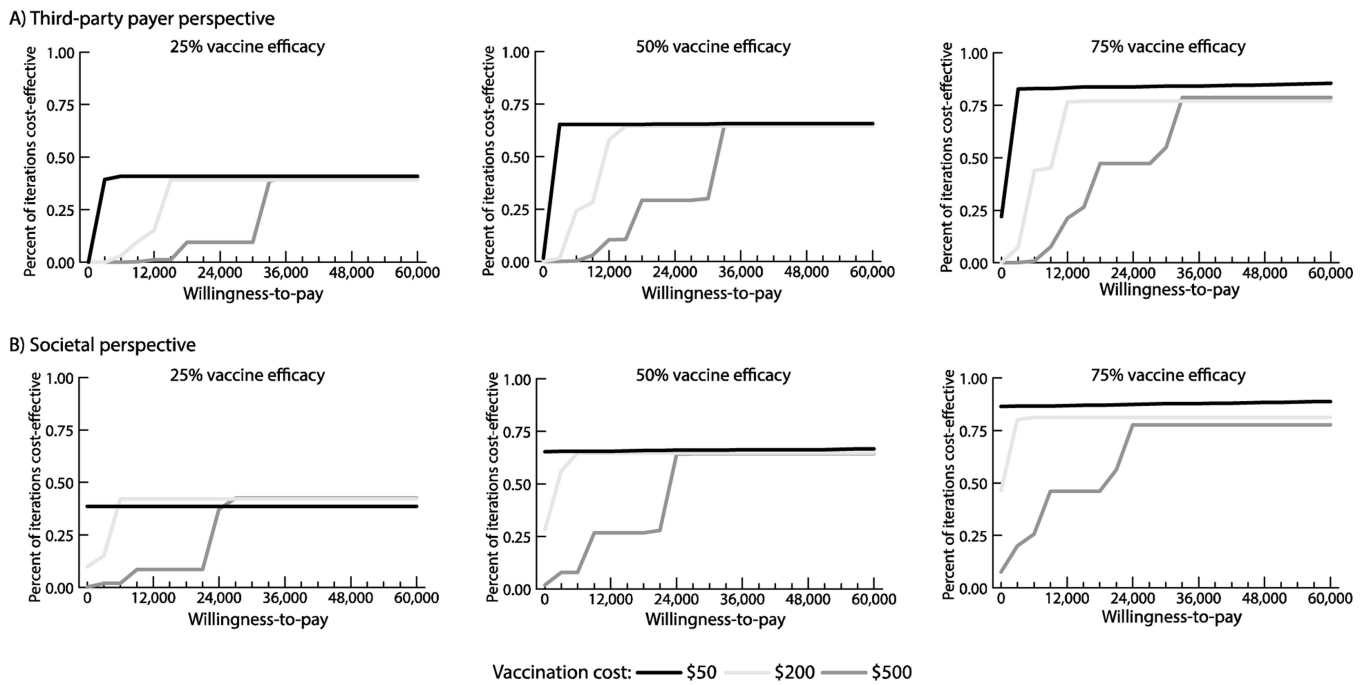| Parameter	Distribution Type	Mean or Median	Standard Deviation or Range[*]	Source
Costs (2019 $US)				
Minor vaccine side effects for the mother (paracetamol)	triangular	2.17	1.31–2.51	[22]
Serological testing algorithm	point estimate	43.52		[54]
Micromethod diagnostic test	point estimate	5.09		[54]
Benznidazole (100mg)	uniform		0.128–0.3134	[55]
Minor benznidazole treatment side effects (antihistamines)	triangular	2.19	0.77–5.25	[22]
NICU bed day	gamma	167.47	45.86	[56]
Follow-up visit	point estimate	40.69		[31]
Daily income[§]	point estimate	23.12		[27]
Lifetime cost per chronic Chagas disease case in Latin				
America				
Third-party payer perspective	triangular	3,198	2,418 – 3,731	[33]
Societal perspective	triangular	29,818	14,051	[33]
Probabilities (annual)				
Minor adverse reaction to the vaccine in pregnant women	point estimate	0.27		[57, 58]
Congenital transmission (current estimate)	triangular	0.05	0.04–0.06	[7]
Symptomatic infant given Chagas infection	beta	0.376	0.158	[10, 12, 59–61]
Symptomatic infant has severe disease	point estimate	0.371		[10, 59–61]
Symptomatic infant has moderate disease	point estimate	0.629		[59–61]
Chagas-related mortality at birth (within 24 hours)	point estimate	0.041		[10, 59, 60]
Preterm birth given infected infant	uniform		0.125–0.194	[59, 62]
Preterm birth given non-infected infant (by gestational age)				
<28 weeks	point estimate	0.05		[63]
28–31 weeks	point estimate	0.15		[63]
32–33 weeks	point estimate	0.2		[63]
34–36 weeks	point estimate	0.6		[63]
Preterm infant mortality (by gestational age)				
<28 weeks	triangular	0.53	0.23–0.75	[64]
28–31 weeks	triangular	0.26	0.08–0.51	[64]
32–33 weeks	triangular	0.1	0.03–0.14	[64]
34–36 weeks	triangular	0.0092	0.001–0.016	[65]
Sensitivity of micromethod test	beta	0.29	0.148	[10, 59, 66–69]
Specificity of micromethod test	point estimate	1		[10, 59, 66–69]

Parameter	Distribution Type	Mean or Median	Standard Deviation or Range*	Source
Infant returns for follow-up visit	gamma	0.422	0.185	[59, 67, 68, 70]
Sensitivity of IgG serology 8 months old	point estimate	1		[10, 71]
Specificity of IgG serology 8 months old	triangular	0.982	0.96–1.00	[10, 71]
Minor adverse event related to benznidazole treatment	beta	0.088	0.146	[1, 12, 25, 69, 72, 73]
Infant completed >80% of benznidazole regimen	beta	0.922	0.114	[1, 12, 25, 68, 69, 72, 73]
Infant that completes treatment will be cured	beta	0.975	0.044	[1, 12, 25, 68, 69, 73]
Progressing to chronic Chagas disease	uniform		0.2 – 0.3	[34, 35]
Durations				
Severe symptoms (not preterm)	point estimate	30 days		Expert opinion
Moderate symptoms (not preterm)	point estimate	7 days		Expert opinion
NICU stay for preterm infants who survive (by gestational age)				
<28 weeks	triangular	116	97–138	[64]
28–31 weeks	triangular	86	66–108	[64]
32–33 weeks	triangular	49	40–60	[64]
34–36 weeks	triangular	16	12–22	[65]
NICU stay for preterm infants who die (by gestational age)				
<28 weeks	triangular	16	7–39	[64]
28–31 weeks	triangular	24	8–59	[64]
32–33 weeks	triangular	21	2–73	[64]
34–36 weeks	triangular	16	12–22	[65]
Disability Weights [§§]				
Severe symptoms	triangular	0.133	0.088–0.190	[32]
Moderate symptoms	triangular	0.052	0.034–0.076	[32]
Infant Weight, Full Term (kg)				
At birth	gamma	3.157	0.477	[74]
At 8 months for males	gamma	8.91	1	[75]
At 8 months for females	gamma	8.49	1	[75]

Note: ELISA=enzyme-linked immunosorbent assay. NICU=neonatal intensive care unit.

[§] 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.

[§§] Due to the lack of specific disability weights related to congenital Chagas, we assumed that acute encephalitis served as a proxy for severe symptoms in infants and moderate anemia due to neglected tropical disease served as a proxy for moderate symptoms.

[*] Variation in parameter values were based on data availability and variability reported in the literature.

Table 2.

Clinical outcomes [mean (95% uncertainty interval)] and total costs (net present value; $US in millions) among 10,000 Chagas-infected pregnant women at current transmission risk estimates (distribution with a median of 5%, range 4% to 6%) for various vaccination strategies

	Number of Congenital Cases	Number of Infant Deaths	Number of Infants that Can Progress to Chronic Disease	Disability-Adjusted Life Years	Total Cost*		Incremental Cost-Effectiveness Ratio (ICER)^	
					Third-Party Payer Perspective	Societal Perspective	Third-Party Payer Perspective	Societal Perspective
No vaccination	500 (405–600)	8 (0–20)	229 (145–330)	313.8 (0.7–750.9) **$50 vaccination**	1.0 (0.7–1.2)	3.8 (0.9–11.4)	-	-
25% efficacy	375 (290–460)	6 (0–20)	172 (100–250)	235.7 (0.5–600.8)	1.3 (1.1–1.6)	3.4 (1.3–6.8)	4,648	Dominant
50% efficacy	249 (185–320)	4 (0–15)	115 (60–190)	154.0 (0.2–450.4)	1.2 (1.0–1.4)	2.6 (1.1–5.4)	1,438	Dominant
75% efficacy	125 (80–170)	2 (0–10)	57 (20–110)	75.7 (0.1–300.2) **$100 vaccination**	1.0 (.9–1.2)	1.8 (1.0–3.8)	357	Dominant
25% efficacy	374 (290–460)	6 (0–20)	172 (100–255)	221.4 (0.5–600.6)	1.8 (1.6–2.1)	4.0 (1.8–7.4)	11,175	2,071
50% efficacy	250 (180–320)	4 (0–15)	115 (60–190)	153.8 (0.2–450.5)	1.7 (1.5–1.9)	3.1 (1.6–5.8)	4,622	Dominant
75% efficacy	126 (80–175)	2 (0–10)	58 (20–110)	78.1 (0.1–300.2) **$200 vaccination**	1.5 (1.4–1.7)	2.3 (1.5–4.3)	2,556	Dominant
25% efficacy	376 (295–460)	6 (0–20)	173 (100–255)	231.1 (0.5–600.6)	2.8 (2.6–3.1)	5.0 (2.8–8.4)	24,341	13,859
50% efficacy	249 (185–320)	4 (0–15)	115 (55–190)	151.3 (0.3–450.4)	2.7 (2.5–2.9)	4.1 (2.6–6.9)	10,988	1,945
75% efficacy	125 (75–175)	2 (0–10)	57 (20–115)	74.5 (0.1–300.2) **$500 vaccination**	2.5 (2.4–2.7)	3.3 (2.5–5.4)	6,981	Dominant
25% efficacy	373 (320–550)	6 (0–50)	172 (100–255)	228.6 (0.7–1,500.0)	5.8 (5.6–6.1)	8.0 (2.9–13.3)	63,528	51,900
50% efficacy	250 (205–460)	4 (0–25)	115 (60–190)	150.3 (0.4–900.0)	5.7 (5.5–5.9)	7.1 (2.7–10.5)	29,040	20,811
75% efficacy	125 (95–205)	2 (0–20)	58 (20–115)	79.6 (0.1–600.0)	5.5 (5.4–5.7)	6.3 (2.5–9.2)	19,352	10,742

*
In millions of $US; Cost includes only those incurred during infancy and excludes lifetime costs associated with chronic Chagas disease.

^
ICER is cost per disability adjusted life year averted; ICERs $9,989/DALY averted are considered highly cost-effective, ICERs between $9,990–29,697/DALY averted are considered cost-effective, ICERs $9,990–29,697/DALY averted are considered cost-effective, ICERs >$29,697/DALY averted are considered not cost-effective; dominant = less costly and provides health benefits.

Table 3.

Number of infants progressing to chronic Chagas disease per 10,000 infants born to Chagas-positive women [mean (95% uncertainty interval)] and their lifetime costs ($US) for various vaccination strategies (assuming the current transmission risk estimate, a distribution with a median of 5%, range 4% to 6%)

	Number of Infants that Can Progress to Chronic Disease	Number of Infants that Progress to Chronic Disease	Lifetime Third-Party Payer Cost	Lifetime Societal Cost
No Vaccination	229(145–330)	56 (34–89)	174,299 (103,270–279,162)	1,610,458 (808,222–2,905,913)
Vaccination				
25% efficacy	172 (100–250)	43 (24–67)	131,765 (70,483–213,175)	1,207,374 (580,993–2,212,298)
50% efficacy	115 (60–190)	29 (14–50)	88,231 (43,790–157,315)	803,707 (357,043–1,627,632)
75% efficacy	57 (20–110)	14 (5–29)	42,847 (14,883–91,089)	391,647 (128,841–911,751)