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The potential economic value of a cutaneous leishmaniasis vaccine in seven endemic countries in the Americas

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ABSTRACT

Cutaneous leishmaniasis (CL) and its associated complications, including mucocutaneous leishmaniasis (MCL) and diffuse CL (DCL) have emerged as important neglected tropical diseases in Latin America, especially in areas associated with human migration, conflict, and recent deforestation. Because of the limitations of current chemotherapeutic approaches to CL, MCL, and DCL, several prototype vaccines are in different states of product and clinical development. We constructed and utilized a Markov decision analytic computer model to evaluate the potential economic value of a preventative CL vaccine in seven countries in Latin America: Bolivia, Brazil, Colombia, Ecuador, Mexico, Peru, and Venezuela. The results indicated that even a vaccine with a relatively short duration of protection and modest efficacy could be recommended for use in targeted locations, as it could prevent a substantial number of cases at low-cost and potentially even result in cost savings. If the population in the seven countries were vaccinated using a vaccine that provides at least 10 years of protection, an estimated 41,000–144,784 CL cases could be averted, each at a cost less than the cost of current recommended treatments. Further, even a vaccine providing as little as five years duration of protection with as little as 50% efficacy remains cost-effective compared with chemotherapy; additional scenarios resembling epidemic settings such as the one that occurred in Chaparral, Colombia in 2004 demonstrate important economic benefits.

1. Introduction

An estimated 1–1.5 million new cases of cutaneous leishmaniasis (CL), a parasitic infection transmitted to humans by the phlebotomine sand fly, occur each year worldwide [1]. Approximately 62,000 of these cases occur in South and Central America and the Caribbean [2]. In recent decades, the incidence of human infection has increased, largely due to human migration, deforestation, urbanization, and adaptation of the *Leishmania* parasite to additional vectors and mammalian hosts [3]. Movement of populations due to conflict and narcotics trafficking has also emerged as a risk factor for CL in Latin America [4]. CL infection usually leads to the appearance of skin lesions within several weeks, which typically self heal in months to years [5]. Approximately a dozen *Leishmania* species causing cutaneous disease are present in South and Central America. CL is sometimes associated with severe chronic outcomes [6]. While cutaneous lesions may heal spontaneously without treatment, infection with some *Leishmania* species may spread to the nasal mucosa or disseminate to multiple locations on the body many years after initial infection. Mucocutaneous leishmaniasis (MCL) rarely heals if untreated, often resulting in severe scarring and death [7]. Ninety percent of MCL cases globally occur in Bolivia, Brazil, and Peru [8], making the

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disease of significant public health importance regionally. Selected *Leishmania* species can also cause diffuse CL (DCL), where non-ulcerative parasite-positive nodules disseminate throughout the body [5]. DCL is usually resistant to treatment and does not self-cure.

Although several drugs are available for CL treatment, many have limitations. The World Health Organization (WHO) recommends pentavalent antimonials as the first line treatment for CL [9]. More recently, liposomal amphotericin B, miltefosine, and other agents have emerged as attractive alternative chemotherapies [10,11]. Despite the high efficacy against CL associated with these drugs, lengthy treatment regimens and toxic drug side-effects may prevent completion of a full treatment regimen. Furthermore, the effectiveness of these treatments against MCL and DCL is less clear.

As an alternative to new chemotherapies, several preventative and therapeutic vaccines for CL are now in different stages of product and clinical development [12–14]. For CL, this alternative appears feasible, as most recovered CL cases are resistant or do not present clinical manifestations of CL to subsequent infections [13]. Subunit vaccines encoding *Leishmania* antigens and epitopes [14] are of particular interest; several vaccines comprised of sand fly salivary proteins alone or in combination with *Leishmania* antigens are under development [15]. For leishmaniasis, there is strong evidence that immunity to a salivary protein from the vector adversely impacts parasite survival and growth contributing to control of the disease [16,17]. Our group is pursuing a prototype vaccine against CL caused by *L. mexicana* infections in Mesoamerica (i.e., southern Mexico and Central America), which is comprised of a recombinant parasite-derived nucleoside hydrolase (NH 36, Chale-Balboa et al. [18]), together with one or more antigens from the sand fly of the genus *Lutzomyia* [19].

Evaluating the potential economic value of a vaccine early in development can help shape the vaccine's characteristics and prepare for successful and timely market release. While some living in CL-endemic countries could undoubtedly benefit from a vaccine, the most appropriate price and target population for the vaccine is less clear. We constructed an economic model of CL infection to delineate the vaccine cost and infection risk required for a preventative vaccine to be beneficial under a range of possible vaccine profiles (i.e., vaccine efficacy, duration of protection, etc.).

2. Methods

2.1. Model structure

We constructed a Markov decision analytic computer simulation model in TreeAge Pro 2009 (TreeAge Software, Williamstown, MA) to evaluate the potential economic value of a cutaneous leishmaniasis vaccine from the societal perspective in seven endemic countries in Latin America: Bolivia, Brazil, Colombia, Ecuador, Mexico, Peru, and Venezuela. Individuals entered the model before they reached one year of age; those vaccinated were offered all doses of the vaccine within the first year, with no attenuated CL risk until completion of the full vaccine regimen. All individuals continued to cycle in the model until death unrelated to leishmaniasis. Each year, individuals had probabilities of transitioning away from or remaining in one of five mutually exclusive Markov states:

- *Uninfected*: Individual was healthy and uninfected.
- *Cutaneous leishmaniasis* (*CL*): Individual was currently infected with CL, developed one or more skin lesions, and only stayed in this state for one year.
- *Mucocutaneous leishmaniasis* (*MCL*): Individual contracted a more severe disease manifestation usually secondary to CL infection, affecting the oral and nasal mucosa. For this disease outcome, scarring is common and disease rarely resolves without treatment. Those affected remained in this state until cured with no relapse or death.
- *Diffuse cutaneous leishmaniasis* (*DCL*): Individual contracted a more severe disease manifestation usually secondary to the CL infection, where skin lesions are widely distributed across the body. Those affected remained in this state until cured with no relapse or death.
- *Prior infection*: Individual had recently recovered from CL, MCL, or DCL and was at risk for MCL and DCL [20,21]. Individuals remained in this state for 10 years (or until they died or developed CL, DCL, or MCL), before returning to be uninfected.
- *Death*: Individual died of causes unrelated to leishmaniasis and ceased to cycle through the model.

Fig. 1a–e shows all transition possibilities between states as well as state-specific events, such as treatment, treatment cure, and reinfection. For instance, a CL case could seek treatment and be cured, in which case the duration of their disease was shorter than those not cured by treatment; CL episodes were assumed to last one year or less [22]. Those recovering from CL had a risk of developing *Leishmania* strain-specific outcomes such as MCL (approximately 2%) or DCL (approximately 5%) shown in Table 1. Individuals had a possibility of multiple CL episodes, assuming any subsequent infection was a different *Leishmania* strain.

Vaccination occurred at month 0 and 1 for the 2-dose presentation (baseline scenarios) and month 0, 1, and 6 for the 3-dose presentation in the model, where everyone received the first dose of vaccine. Receipt of subsequent doses depended on compliance; no protection was granted until completion of full vaccine regimen. CL risk in the model depended upon a person's vaccination status. A 3% discount rate [23] converted all costs to 2012 US$ and future costs to their 2012 value.

2.2. Model parameters

We conducted a literature review on cutaneous leishmaniasis in the Americas using MEDLINE and the following terms: [cutaneous leishmaniasis], [tegumentary leishmaniasis], [leishmaniasis treatment], [mucocutaneous leishmaniasis], [diffuse cutaneous leishmaniasis], and [cutaneous leishmaniasis vaccine]. Countries selected were chosen based on the completeness of available data. Data from the year 2000 on were used if available. Table 1 contains a list of model parameters and their sources. Country-specific breakdowns of *Leishmania* by species [24] were used to estimate the likelihood of clinical outcomes such as MCL, DCL, spontaneous cure, and illness duration. Although recent reports suggest little change in *Leishmania* species distribution has occurred over the past 20 years [25,26] in some regions, changes in species distribution over time may cause the risk of species-dependent outcomes (i.e., MCL and DCL) to deviate from our estimates.

CL cases had a 20–60% likelihood of seeking treatment; those with MCL or DCL had a 40–100% (~2 times greater) chance of receiving treatment. CL cases were initially given 20 mg/kg of pentavalent antimonials for 20 days, as recommended by the WHO [9], and were retreated with either pentamidine or pentavalent antimonials upon treatment failure [27]. Cases were not retreated after experiencing two treatment failures. Pentavalent antimonials (30 day regimen) were used to treat those with DCL and MCL initially, while pentamidine and amphotericin B were administered if disease persisted