Comparative study of Chagas disease seroprevalence in pregnant women from endemic regions attended at Hospital General de Mexico (Mexico City, Mexico) and Johns Hopkins Bayview (Baltimore, USA)

Executive Summary

This report shares our findings from our cross-sectional study on Chagas disease among pregnant women in the United States and Mexico. The study objectives were to (i) ascertain and compare seroprevalence of *Trypanosoma cruzi* infection in pregnant women and (ii) assess the performance of a rapid, point-of-care diagnostic test in both populations.

Policy recommendations are:

- There is a need for screening processes particularly among pregnant women from endemic areas.
- WHO/PAHO positive diagnostic criteria need to be refined to specify which tests are appropriate for the circulating *T. cruzi* lineages (Discrete Typing Units (DTUs)).
- At-risk populations should undergo greater monitoring and surveillance for Chagas disease.

We anticipate findings from our study will support policies that aim to improve screening of Chagas disease among high-risk women in the US and Mexico.

Introduction

Chagas disease is a significant, yet neglected tropical infection, infecting more than 7.5 million people worldwide (Lee *et al*., 2013). It is endemic to the Americas, where the Chagas parasite *Trypanosoma cruzi* is transmitted to humans by triatominae ("kissing bug" or "chinche") or mother-to-child during pregnancy. In non-endemic areas like the US, prevalence is attributable to migration, expansion of the vector spurred by climate change, and congenital transmission among immigrant women.

Congenital transmission has been associated with increased risk of perinatal complications such as low Apgar scores, low birthweight, premature birth, and miscarriage. Congenital Chagas is estimated to account for 22% of all new infections (Messenger *et al*., 2017). In the US, 50% of immigrants from Mexico are from Chagas endemic states and bear the burden of its cardiovascular complications. Transmission has been reported via heart transplantations and blood banks in Los Angeles (anon, n.d.; Shulman, et al., 1997). Additionally, it has been diagnosed in infants born in California, suggesting congenital transmission (anon, 2019; Kun *et al*., 2009).

Diagnosis of Chagas disease is complicated by the plethora of laboratory tests, many of which are not readily available in most clinical settings (Stanaway and Roth 2015).

Because of genetic diversity of *T. cruzi*, the sensitivity of confirmatory laboratory test varies by region and test (Schaeubinger *et al*., 2019). Additionally, there is a lack of awareness of Chagas disease in both healthcare providers and patients (Sanchez *et al*., 2014; Stimpert & Montgomery, 2010). As a consequence, less than 1% of patients with Chagas disease worldwide get treatment, complicating the identification of pregnant women who may be at risk of transmitting the parasite to their offspring (Picado *et al*., 2017).

Study

Our cross-sectional comparative study is spearheaded by an interdisciplinary team of researchers from the University of Arizona, Universidad Nacional Autónoma de México (UNAM), San Diego State University and Johns Hopkins University (JHU). The objectives of this study were to ascertain and compare seroprevalence of *T. cruzi* infection in pregnant women in the US and Mexico, and to assess the performance of a rapid, point-of-care diagnostic test in both populations.

Prevalence of Chagas Disease

Very few studies have evaluated the seroprevalence of Chagas disease in the US and in Mexico, and the current burden of Chagas remains essentially unknown. It is estimated that the Chagas prevalence in the US ranges from 0.007 to 1.3%. However, in Mexico, an area widely regarded as endemic, estimated national averages (.92%, 1.6%, 2.26%) are misrepresented by the wide variation in local prevalence seen across the country ranging from 0.36% to 20.0%.

Targeted Study Population

Testing activities were targeted at a high-risk population of Latina women presenting at Care-A-Van (Johns Hopkins Bayview Medical Center, Baltimore, Maryland) and the Obstetrics and Gynecology Ward of the Mexican General Hospital, Medical Faculty (Universidad Nacional Autónoma de México, Mexico City, Mexico). A cumulative 296 patients were tested and the PAHO/WHO standard of two independent tests -- here we used PCR and any other serological test -- to define positive. In Baltimore, Chagas was undetected among the 146 participants. In Mexico, 150 patients were analyzed and 8 (5.3%) were positive.

Unsurprisingly, among the positive tests in Mexico, results were highly discrepant, across different tests used. Nine patients (7.5%) were positive by the most specific test alone (PCR). When compared to serologic tests, none were positive by Accutrack ELISA, six were positive by the FDA-approved InBios, and six were positive and three indeterminate by the in-house ELISA.

Healthy Policy Impact

Evaluating *T. cruzi* infection has the potential to support policy to address health concerns both in Mexico and the US while providing financial benefit.

1) There is a need for screening processes, particularly among pregnant women from endemic areas.

Our Mexican cohort consisted of pregnant women who sought prenatal care in the Hospital General de Mexico. This is the main reference hospital for the uninsured in Mexico and serves local, Mexico City residents as well as women referred because of high risk pregnancies. While the sample size is small, all of the positive women in our sample had lived in endemic areas. The positive results are indicative of continuing undetected Chagas transmission. Currently, pregnant women are not routinely screened for *T. cruzi* infection, despite the benefits for their own personal well-being as well as that of their child. Early detection is particularly important among infants, as it provides a unique opportunity to provide treatment that definitively clears the infection.

In Latin America, the current standard for diagnosis of congenital *T. cruzi* infection in infants is 1) the 'micromethod' (microscopy of concentrated cord blood); 2) hemocultures.; and 3) gold standard serologic tests starting at 8-12 months of age; or seroconversion, in the case of suspected acute infection with another mode of transmission . However, the micromethod is time-consuming, labor-intensive, and unreliable; standard serologic tests are reliable only after maternal antibodies have waned, 8 to 12 months after birth. Testing is not sensitive and there is poor compliance in follow-up.

There are no assays that are at present available commercially and there is still a pressing need for a simple, sensitive and specific rapid strip assay that can screen babies born to a mother from an endemic area. This test should function for all *T. cruzi* lineages (DTUs).

2) WHO/PAHO positive diagnostic criteria need to be refined to specify which tests are appropriate for the circulating *T. cruzi* lineages (Discrete Typing Units (DTUs))

The presence of Chagas disease in the US and Mexico is characterized by different lineages of the parasite that may require different diagnostic procedures. This becomes important in a mixed lineage environment, particularly given the large genetic diversity of the parasite (classified by seven DTUs).

Our study shows it is imperative that the test match the predominant *T. cruzi* lineages in the affected population. Most currently commercially available serologic tests were developed in other endemic settings (e.g. South America) where different lineages predominate.

We highlight the need for standardized guidelines for diagnosis and testing according to the predominant lineage, and describe current low specificity and sensitivity of available diagnostic tools.

3) At-risk populations should undergo greater monitoring and surveillance for Chagas disease

Our study showed that while overall disease prevalence is low, in selected groups, there is a need to initiate screening and follow-up processes when appropriate.

Strengthening access to healthcare is crucial to obtaining adequate screening for Chagas disease. One suggested approach at country level is to develop initiatives

tailored to the local health system and in alignment with general health goals and programs. Such is the case of Mexico and the Specific Action Program for the Prevention and Control of Chagas Disease 2013-2018. A primary care-based screening pilot program in Boston found 3.8% positive screening tests is an example of the feasibility of the incorporation of Chagas disease screening in primary care in non-endemic settings. These examples show how custom-made interdisciplinary initiatives that align with local goals and health projects are feasible, effective, and should be promoted to screen as many people as cost-effectively as possible in primary care settings.

Future Directions

This study showed that it is important to revise current diagnostic algorithms for different scenarios with diverse *T. cruzi* lineages. For example, the lack of positive diagnoses in patients among the samples from Baltimore may be due to a mis-alignment between the test and predominant *T. cruzi* lineages circulating. Furthermore, this study provides evidence for the necessity of prenatal screening of women from Chagas-endemic areas.

Promising tests that could be incorporated into future studies include molecular assays for detection of congenital infection in babies. There is also a need to develop highly specific serological tests that can be easily implemented in community settings.

Taken together, this project combined experts and institutions to evaluate Chagas disease in pregnant women from endemic regions seen at the Hospital General de Mexico and in migrants, largely coming from Honduras, El Salvador, and Mexico, at Johns Hopkins. This opens an important window of opportunity for the detection of Chagas disease in women and an early treatment opportunity for children, at a stage when the disease is curable with a low side effect profile.

References

Anonymous, (n.d.). Chagas Disease After Organ Transplantation—Los Angeles, California, 2006. Retrieved July 26, 2019, from https://www.cdc.gov/mmwr/preview/mmwrhtml/mm5529a3.htm

Anonymous, (2019, June 3) Immigrants in America: Key Charts and Facts | Pew Research Center. Retrieved July 24, 2019, from https://www.pewhispanic.org/2019/06/03/facts-on-u-s-immigrants/

Kun, H., Moore, A., Mascola, L., Steurer, F., Lawrence, G., Kubak, B., … Chagas Disease in Transplant Recipients Investigation Team. (2009). Transmission of Trypanosoma cruzi by heart transplantation. *Clinical Infectious Diseases: An Official Publication of the Infectious Diseases Society of America*, *48*(11), 1534–1540. https://doi.org/10.1086/598931

Lee, B. Y., Bacon, K. M., Bottazzi, M. E., & Hotez, P. J. (2013). Global economic burden of Chagas disease: a computational simulation model. The Lancet infectious diseases, 13(4), 342-348.

Messenger LA, Gilman RH, Verastegui M, et al. Towards improving early diagnosis of congenital Chagas disease in an endemic setting. Clin Infect Dis. 2017.

Picado, A., Angheben, A., Marchiol, A., Alarcón de Noya, B., Flevaud, L., Pinazo, M. J., … Moriana, S. (2017). Development of Diagnostics for Chagas Disease: Where Should We Put Our Limited Resources? *PLoS Neglected Tropical Diseases*, *11*(1). https://doi.org/10.1371/journal.pntd.0005148

Sanchez, D. R., Traina, M. I., Hernandez, S., Smer, A. M., Khamag, H., & Meymandi, S. K. (2014). Chagas Disease Awareness among Latin American Immigrants Living in Los Angeles, California. *The American Journal of Tropical Medicine and Hygiene*, *91*(5), 915–919. https://doi.org/10.4269/ajtmh.14-0305

Schaeubinger, M., Chakravarti, I., Lidani, K. C. F., Omidian, Z., and Gilman, R. H. (2019). Systematic Review of the Epidemiology of Chagas Disease in the Americas: a Call for Standardized Reporting of Chagas Disease Prevalence. Current Tropical Medicine Reports, 1-12.

Shulman, I. A., Appleman, M. D., Saxena, S., Hiti, A. L., & Kirchhoff, L. V. (1997). Specific antibodies to Trypanosoma cruzi among blood donors in Los Angeles, California. *Transfusion*, *37*(7), 727–731.

Stanaway, J. D., & Roth, G. (2015). The burden of Chagas disease: estimates and challenges. Global Heart, 10(3), 139-144.

Stimpert, K. K., & Montgomery, S. P. (2010). Physician Awareness of Chagas Disease, USA. *Emerging Infectious Diseases*, *16*(5), 871–872. https://doi.org/10.3201/eid1605.091440