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Opportunities and Challenges in Chronic Chagas Cardiomyopathy

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Chronic Chagas cardiomyopathy (CCC) is the most serious complication of Chagas disease. More than a century after the astute clinician-scientist Carlos Chagas published the etiologic, pathological, clinical, and epidemiological characteristics of the disease that now bears his name [1], much scientific progress has been made. Nevertheless, many challenges still remain. In this article, we provide a brief perspective on the clinical and public health successes as well as a summary of the biomedical research portfolio supported by the National Heart, Lung, and Blood Institute (NHLBI). Finally, we explore the compelling research questions and critical challenges for better understanding CCC and tackling its prevention and treatment.

SUCCESSES IN CHAGAS DISEASE PREVENTION AND TREATMENT

Carlos Chagas's discovery of the protozoan parasite (*Trypanosoma cruzi*) that caused nonmalarial febrile illness in Brazilian railroad workers and his subsequent meticulous clinical description of the first human case of Chagas disease are now legendary [2,3]. Subsequent molecular characterization of *T. cruzi*, its insect vector (*Triatoma infestans*) and reservoirs, and various modes of non-vector-related transmission have provided significant insight about the parasite and the host-parasite and parasite-vector interactions since its discovery [4–6]. Additional research advances have increased our understanding of the acute and chronic phases of the disease; the multisystem impact of the disease resulting in gastrointestinal, neurologic, and thromboembolic events; as well as the spectrum of cardiac involvement including myocarditis with or without pericardial effusion, electrophysiological derangements, and severe cardiomyopathy with frank systolic heart failure [7–9].

Trypanosoma cruzi belongs to an ancient family of kinetoplastid organisms, a group of flagellated protozoa that parasitize virtually all animal groups as well as plants and insects. These parasites have diverse morphology, intriguing mechanisms for control of gene

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expression, and complex digenetic life cycles involving a human host, animal reservoir, and insect vector [10,11]. With genomic sequencing of *T. cruzi*, completed in 2005, much interest in the complex trypanosome biology has developed. The complexity of *T. cruzi*'s genetic variation and its ability to escape host immune responses is under ongoing investigation [12–14]. This genetic variability is presumably a significant contributing factor to its widespread enzootic infection. Distribution of *T. cruzi* genetic signatures from infections throughout the mammalian fauna indicates that it has more animal reservoirs than was previously understood [15].

Vector transmission is now known to be most common via *Triatoma infestans*, the primary domestic vector of *T. cruzi* in rural areas of Brazil, Chile, Uruguay, Argentina, Bolivia, and Paraguay, and also by *Rhodnius prolixus*, in rural areas of Guatemala, Honduras, and El Salvador [16]. Chagas disease can also be transmitted congenitally and orally through the ingestion of triatomine-contaminated foods and drinks, as well as via blood transfusion, organ transplantation, and accidental needle-sticks [17–22]. The oral route as an avenue of transmission was important in several outbreaks in Brazil, Colombia, and Venezuela, where ingestion of food contaminated with *T. cruzi* led to illness [21]. These research efforts have contributed several important advances in our understanding of the host-pathogen interaction and related inflammatory and immune responses.

We also know the characteristic features of acute and chronic phases of infection with *T. cruzi*. The acute phase of Chagas disease is marked by variable symptomatology consistent with a nonspecific, self-limiting acute febrile illness that is recognized in only 1% to 2% of infected persons [23]. When present, these symptoms typically decline after 4 to 8 weeks [23]. Parasitemia, which can be detected during the acute phase, can also be eliminated with appropriate treatment. Mortality in the acute phase is rare and estimated to be <1%. In patients who develop the chronic phase of Chagas disease, the majority remains asymptomatic, but 30% of seropositive individuals progress to the development of CCC, digestive megasyndromes, and/or central nervous system complications [7–9,23]. Among the important manifestations of CCC are heart failure, atrial and ventricular arrhythmias, sudden cardiac death, and thromboembolic events in the systemic and pulmonary circulations.

In addition to the fundamental biomedical research discoveries that shed light on these various clinical and laboratory phenomena, several successful national and regional public health initiatives in the prevention and control of Chagas disease have occurred. The most successful of these programs—all executed in the 1990s—include the Southern Cone Initiative [24–26], the Andean Pact Initiative [26–28], and the Central America Initiative [26,28–31]. Through these initiatives, efforts to eradicate large populations of domestic vectors and their reservoirs were made, blood donors were screened to increase blood safety and prevent transfusion-related transmission, and maternal screening was increased to reduce congenital transmission and improve early detection and treatment of infected newborn babies [24–31].

Barely 3 decades ago, about 100 million people (over 25 million in Brazil alone) were considered at risk for *T. cruzi* infection [23,32]. However, by the dawn of the 21st century,

the Pan American Health Organization certified that *T. infestans* had been effectively eliminated from human dwellings not only in Brazil, but also in Chile, Uruguay, and large areas of Argentina, Bolivia, and Paraguay [33]. In fact, transmission of *T. cruzi* by the predominant domestic vectors was “certified as interrupted” in Uruguay in 1997, in Chile in 1999, in Brazil in 2006, and in Guatemala, Honduras, El Salvador, and Nicaragua in 2009 to 2010 [23]. This major public health success led to significant reductions in the number of persons at risk for infection as well as substantial reductions in new cases of Chagas disease and related burden of disability and death [23]. Although, infection via *T. infestans* has been limited due to successful eradication efforts, *T. cruzi* transmission also commonly occurs via the oral route, and it is estimated that 6 million to 7 million people are infected with *T. cruzi* worldwide [34].

At the patient level, advances in antitrypanosomal treatment and adjunctive therapy for the management of cardiovascular, gastrointestinal, and neurological symptoms and complications represent clinical successes. However, only 2 drugs (benznidazole and nifurtimox) are available and recommended for the treatment of Chagas disease [23,35–40]. In the United States, these drugs are not approved by the Food and Drug Administration and can only be obtained for use from the Centers for Disease Control and Prevention under investigational protocols [41]. Adverse side effects to both medications are relatively common and have been shown to be more frequent and more severe with advancing age [41].

For end-stage CCC, cardiac transplantation is an option, yet mortality rates remain high. In a series of 107 cases of cardiac transplantation in Brazil [42], in-hospital mortality was 17.7% with a late mortality of 25.2%. Stem cell-based therapies are also being evaluated in pre-clinical and clinical studies [43]. However, the initial promising results seen in animal models have not been demonstrated in early human clinical trials [43].

NHLBI-FUNDED RESEARCH ON CHAGAS DISEASE

The significant global burden of Chagas disease necessitates ongoing research efforts to increase understanding of mechanisms, develop effective treatments, and improve prevention. NHLBI recognizes this need and is committed to ongoing support of research on Chagas disease. Although the burden of Chagas disease is significant, relatively few grant applications have been submitted to NHLBI in this area over the past decade. NHLBI supported 16 grants focused on Chagas disease from 2005 to 2015. These grant applications used a variety of approaches, including animal studies, human genetics, clinical research, stem cell biology, technology development, and bioinformatics. NHLBI’s portfolio of funded research on Chagas disease is diverse and multifaceted; it includes studies aimed at understanding mechanisms, improving diagnosis, developing treatments, and enhancing prevention.

For example, NHLBI-funded investigators have explored mechanisms of parasite transmission and survival and mechanisms of the subsequent development of cardiomyopathy. Leon et al. [44] explored autoimmunity in Chagas disease, whereas Unnikrishnan and Burleigh [45] identified mechanisms by which *T. cruzi* interferes with the

fibrotic response of the host, and Ba et al. [46] and Wen et al. [47] characterized various reactive oxygen species and inflammatory responses to *T. cruzi*. Other mechanistic studies have focused on the role of lipid metabolism in infection and the subsequent development of CCC. Johndrow et al. [48] demonstrated that *T. cruzi* induces increases in intracellular low-density lipoprotein and cholesterol in murine models during the acute and chronic phases of infection by up-regulating the low-density lipoprotein receptor, and they showed similar findings in CCC-affected human heart tissue. Nagajyothi et al. [49] showed that a high fat diet in mice alters the host metabolic regulation, leading to parasite sequestration in adipose tissue and a surprising protective effect of decreased mortality, lower levels of parasitemia, and less myocardial damage during acute infection.

Williams-Blangero et al. [50] was the first to use single nucleotide polymorphism typing in Chagas disease to explore genetic determinants of susceptibility and cardiovascular progression of disease in humans. Research by Wen et al. [51] focused on improving the ability to diagnose Chagas disease identified a proteomic signature for patients with CCC to allow for earlier detection of disease. Another study focused on the development of therapeutic approaches using stem cells as alternatives to transplantation. Goldenberg et al. [52] found that stem cell therapy using bone marrow mononuclear cells reverses cardiac dilation in mice with CCC. NHLBI-funded prevention research on Chagas disease entailed the development of technology and screening tools to improve the safety of the blood supply as well as the implementation of science efforts to decrease the number of high-risk blood donors who may transmit *T. cruzi*. Finally, NHLBI-funded investigators recognized a need to improve access to and integration of existing data on Chagas disease to increase the potential for learning from the extant knowledge base. They used bioinformatic approaches to integrate myriad data sources on Chagas disease and create a resource for investigators [53].

MOVING TO THE FUTURE: PERSISTING CHALLENGES AND BIOMEDICAL RESEARCH QUESTIONS

In spite of the impressive record of biomedical research advances and major clinical and public health successes of the last century in the prevention and control of Chagas disease [3,33,54,55], many important challenges persist. Public health successes have led to a decline in at-risk populations and infected persons in endemic areas. However, there is an emerging rise in the number of *T. cruzi*-infected individuals in the United States and several nonendemic countries in Europe and the Western Pacific region [35–40,56–59]. This represents an important clinical and public health challenge. For example, in the United States Trypanosoma cruzi Infection Study, Cantey et al. [56] reported 16 cases of chronic *T. cruzi* infection presumably acquired via vector-borne transmission in the United States. That study estimated the prevalence of indigenous infections in the United States as 1 in 354,000 blood donors [56].

With increasing globalization, international travel, and migration, there is a concern that large numbers of persons from Chagas disease–endemic countries who may be infected with *T. cruzi* and are unaware of their infection status may lead to a rise in congenital, transfusion- and/or transplant-associated transmission in nonendemic countries [58,60].

Coura and Viñas [60] showed that the *T. cruzi* parasite can travel with population movements from endemic to nonendemic countries in North America, the Western Pacific region, and Europe (Figure 1). In their review [60], they cited estimates of the number of *T. cruzi*-infected persons as >300,000 in the United States, >5,500 in Canada, >80,000 in Europe and in the Western Pacific region, >3,000 in Japan, and >1,500 in Australia.

In 2009, Bern and Montgomery [61] applied published seroprevalence figures to immigrant populations in the United States and estimated that 300,167 individuals with *T. cruzi* infection live in the United States and that 30,000 to 45,000 cardiomyopathy cases and 63 to 315 congenital infections occur annually in the United States. The foci of vector-borne transmissions in the United States and other nonendemic countries are often unknown, thus making it difficult to design tailored public health measures for interrupting transmission. Enhancing diagnosis and treatment for the millions that are affected remains a major challenge. The World Health Organization [62] states that elimination remains the overall goal, but this will require better health surveillance, prevention of blood and organ transplant transmission, better availability of diagnostic tests, prevention of vertical mother to infant transmission, and high-quality case management.

From a biomedical research perspective, several compelling questions also remain unanswered. For example, what determines resilience in chronically infected patients who remain asymptomatic over many years? What signals the transition from the indeterminate stage of CCC to subsequent stages that manifest electrocardiographic abnormalities and eventual biventricular systolic dysfunction and symptomatic heart failure? Are there identifiable myocardial tissue, soluble factors, or biomarkers of adverse prognosis in asymptomatic carriers of the parasite? To what extent does the presence of the carrier state and seropositivity influence myocardial fibrosis and extracellular matrix remodeling that hastens ventricular systolic function impairment and severe heart failure? By what mechanisms, if at all, does *T. cruzi* regulate the expression of fibrotic genes involved in the development of cardiac pathology? What are the kinetics of cellular gene expression, characteristics of gene networks, and protein-protein interactions induced by *T. cruzi*? What role could exercise-induced changes in chronotropic competence or mid-wall left ventricular mechanics play in assessing prognosis in asymptomatic carriers of the parasite? What role do cellular and humoral inflammatory mediators play in disease progression? In what ways could current understanding of the molecular biology of the parasite and the host-parasite interaction inform the discovery of novel vaccines, drugs, diagnostics, and devices for the management of CCC and related complications? Other research questions have been identified in other settings [63–65].

Knowledge gained by studying Chagas disease may have broader applications for other disease states. For instance, understanding the mechanisms of development of fibrosis and cardiomyopathy in Chagas disease may provide insights into fibrosis and progression in other forms of noninfectious cardiomyopathy. For example, work in this arena could help inform research on endomyocardial fibrosis, which is more prominent in sub-Saharan Africa and of unknown etiology. Perhaps repeated exposure to parasitic infections may underlie the pathogenesis of endomyocardial fibrosis. Thus, paradigms developed from Chagas disease research may have far-reaching benefits across the globe. Additionally, strategies developed

and optimized for detection of *T. cruzi* in the blood supply may be applied to other blood-borne pathogens and improve the overall safety of the blood supply. Development of point-of-care devices for such detection may yield a significant public health affect by identifying infected donors in low-resource settings and endemic areas and preventing further transmission.

The NHLBI is committed to “provide global leadership for a research, training, and education program to promote the prevention and treatment of heart, lung, and blood diseases and sleep (HLBS) disorders, and enhance the health of all individuals so that they can live longer and more fulfilling lives” [66]. As a learning organization, NHLBI aims to understand how it can leverage previous efforts and established cohorts to develop innovative multinational, transdisciplinary collaborations to advance knowledge about heart, lung, and blood diseases and sleep disorders globally. This is particularly important now, as NHLBI moves forward with its Strategic Visioning Initiative and launches a new research agenda for the next decade by identifying compelling questions and critical challenges in basic, clinical, translational, and population science research related to heart, lung, blood, and sleep disorders [67].

References

1. Chagas C. Nova entidade mórbida do homem: resumo geral de estudos etiológicos e clínicos [in Portuguese and German]. Mem Inst Oswaldo Cruz. 1911; 3:219–75.
2. The Chagas Disease Foundation. History. 2015. Available at: <http://www.chagasfound.org/chagas-disease-info.php?ID=4&t=History>. Accessed
3. Tibayrenc, M.; Tilleria, J. American trypanosomiasis: Chagas Disease: One Hundred Years of Research. 1. Burlington, MA: Elsevier; 2010.
4. Gurgel-Gonçalves R, Ramalho ED, Duarte MA, et al. Enzootic transmission of *Trypanosoma cruzi* and *T. rangeli* in the Federal District of Brazil. Rev Inst Med Trop Sao Paulo. 2004; 46:323–30. [PubMed: 15654478]
5. Vallejo GA, Guhl F, Schaub GA. Triatominae-*Trypanosoma cruzi*/*T. rangeli*: vector-parasite interactions. Acta Trop. 2009; 110:137–47. [PubMed: 18992212]
6. Guhl F, Jaramillo C, Carranza JC, Vallejo GA. Molecular characterization and diagnosis of *Trypanosoma cruzi* and *T. rangeli*. Arch Med Res. 2002; 33:362–70. [PubMed: 12234526]
7. Nunes MC, Dones W, Morillo CA, et al. for the Council on Chagas Disease of the Interamerican Society of Cardiology. . Chagas disease: an overview of clinical and epidemiological aspects. J Am Coll Cardiol. 2013; 62:767–76. [PubMed: 23770163]
8. Rassi A Jr, Rassi A, Marin-Neto JA. Chagas disease. Lancet. 2010; 375:1388–402. [PubMed: 20399979]
9. Tanowitz HB, Kirchhoff LV, Simon D, Morris SA, Weiss LM, Wittner M. Chagas’ disease. Clin Microbiol Rev. 1992; 5:400–19. [PubMed: 1423218]
10. Gull K. The biology of kinetoplastid parasites: insights and challenges from genomics and post-genomics. Int J Parasitol. 2001; 31:443–52. [PubMed: 11334928]
11. Daniels JP, Gull K, Wickstead B. Cell biology of the trypanosome genome. Microbiol Mol Biol Rev. 2010; 74:552–69. [PubMed: 21119017]
12. El-Sayed NM, Myler PJ, Bartholomeu DC, et al. The genome sequence of *Trypanosoma cruzi*, etiologic agent of Chagas disease. Science. 2005; 309:409–15. [PubMed: 16020725]
13. Zingales B, Miles MA, Campbell DA, et al. The revised *Trypanosoma cruzi* subspecific nomenclature: rationale, epidemiological relevance and research applications. Infect Genet Evol. 2012; 12:240–53. [PubMed: 22226704]

14. Andersson B. The *Trypanosoma cruzi* genome; conserved core genes and extremely variable surface molecule families. *Res Microbiol.* 2011; 162:619–25. [PubMed: 21624458]
15. Jansen AM, Xavier SC, Roque AL. The multiple and complex and changeable scenarios of the *Trypanosoma cruzi* transmission cycle in the sylvatic environment. *Acta Trop.* 2015 E-pub ahead of print.
16. Dias JC, Silveira AC, Schofield CJ. The impact of Chagas disease control in Latin America: a review. *Mem Inst Oswaldo Cruz.* 2002; 97:603–12. [PubMed: 12219120]
17. Howard EJ, Xiong X, Carlier Y, Sosa-Estani S, Buekens P. Frequency of the congenital transmission of *Trypanosoma cruzi*: a systematic review and meta-analysis. *BJOG.* 2014; 121:22–33. [PubMed: 23924273]
18. Sánchez LV, Ramírez JD. Congenital and oral transmission of American trypanosomiasis: an overview of physiopathogenic aspects. *Parasitology.* 2013; 140:147–59. [PubMed: 23010131]
19. Cevallos AM, Hernández R. Chagas' disease: pregnancy and congenital transmission. *Biomed Res Int.* 2014; 2014:401864. [PubMed: 24949443]
20. Benjamin RJ, Stramer SL, Leiby DA, Dodd RY, Fearon M, Castro E. *Trypanosoma cruzi* infection in North America and Spain: evidence in support of transfusion transmission. *Transfusion.* 2012; 52:1913–21. [PubMed: 22321142]
21. Pereira KS, Schmidt FL, Barbosa RL, et al. Transmission of Chagas disease (American trypanosomiasis) by food. *Adv Food Nutr Res.* 2010; 59:63–85. [PubMed: 20610174]
22. Hofflin JM, Sadler RH, Araujo FG, Page WE, Remington JS. Laboratory-acquired Chagas disease. *Trans R Soc Trop Med Hyg.* 1987; 81:437–40. [PubMed: 3120369]
23. World Health Organization. Research priorities for Chagas disease, human African trypanosomiasis and leishmaniasis. *World Health Organ Tech Rep Ser.* 2012; (975):v–xii. 100. [PubMed: 23484340]
24. Schofield CJ, Dias JC. The Southern Cone Initiative against Chagas disease. *Adv Parasitol.* 1999; 42:1–27. [PubMed: 10050271]
25. Elimination of transmission of Chagas disease in southernmost Latin America. *World Health Forum.* 1994; 15:299–300. [PubMed: 7945765]
26. Schofield CJ, Dujardin JP. Chagas disease vector control in Central America. *Parasitol Today.* 1997; 13:141–4. [PubMed: 15275100]
27. Guhl F. Chagas disease in Andean countries. *Mem Inst Oswaldo Cruz.* 2007; 102(Suppl 1):29–38. [PubMed: 17891273]
28. Yamagata Y, Nakagawa J. Control of Chagas disease. *Adv Parasitol.* 2006; 61:129–65. [PubMed: 16735164]
29. Moncayo A. Progress towards the elimination of transmission of Chagas disease in Latin America. *World Health Stat Q.* 1997; 50:195–8. [PubMed: 9477549]
30. Chagas disease. Central American initiative launched. *TDR News.* 1998; (55):6.
31. Guzmán-Bracho C. Epidemiology of Chagas disease in Mexico: an update. *Trends Parasitol.* 2001; 17:372–6. [PubMed: 11685897]
32. Dias JC. Control of Chagas disease in Brazil. *Parasitol Today.* 1987; 3:336–41. [PubMed: 15462880]
33. Bonney KM. Chagas disease in the 21st century: a public health success or an emerging threat? *Parasite.* 2014; 21:11. [PubMed: 24626257]
34. Malik LH, Singh GD, Amsterdam EA. The Epidemiology, clinical manifestations, and management of Chagas heart disease. *Clin Cardiol.* 2015 E-pub ahead of print.
35. Salomon CJ. First century of Chagas' disease: an overview on novel approaches to nifurtimox and benznidazole delivery systems. *J Pharm Sci.* 2012; 101:888–94. [PubMed: 22161779]
36. Coura JR, Borges-Pereira J. Chronic phase of Chagas disease: why should it be treated? A comprehensive review. *Mem Inst Oswaldo Cruz.* 2011; 106:641–5. [PubMed: 22012216]
37. Le Loup G, Pialoux G, Lescure FX. Update in treatment of Chagas disease. *Curr Opin Infect Dis.* 2011; 24:428–34. [PubMed: 21857512]

38. Maya JD, Orellana M, Ferreira J, Kemmerling U, López-Muñoz R, Morello A. Chagas disease: present status of pathogenic mechanisms and chemotherapy. *Biol Res.* 2010; 43:323–31. [PubMed: 21249304]
39. Rodrigues CJ, de Castro SL. A critical review on Chagas disease chemotherapy. *Mem Inst Oswaldo Cruz.* 2002; 97:3–24. [PubMed: 11992141]
40. Urbina JA. Chemotherapy of Chagas disease. *Curr Pharm Des.* 2002; 8:287–95. [PubMed: 11860367]
41. Centers for Disease Control and Prevention. Antiparasitic treatment. Jul 13. 2013 Available at: http://www.cdc.gov/parasites/chagas/health_professionals/tx.html. Accessed
42. Fiorelli AI, Santos RH, Oliveira JL Jr, et al. Heart transplantation in 107 cases of Chagas' disease. *Transplant Proc.* 2011; 43:220–4. [PubMed: 21335192]
43. de Carvalho AC, Carvalho AB. Stem cell-based therapies in chagasic cardiomyopathy. *Biomed Res Int.* 2015; 2015:436314. [PubMed: 26161401]
44. Leon JS, Daniels MD, Toriello KM, Wang K, Engman DM. A cardiac myosin-specific autoimmune response is induced by immunization with *Trypanosoma cruzi* proteins. *Infect Immun.* 2004; 72:3410–7. [PubMed: 15155647]
45. Unnikrishnan M, Burleigh BA. Inhibition of host connective tissue growth factor expression: a novel *Trypanosoma cruzi*-mediated response. *FASEB J.* 2004; 18:1625–35. [PubMed: 15522908]
46. Ba X, Gupta S, Davidson M, Garg NJ. *Trypanosoma cruzi* induces the reactive oxygen species-PARP-1-RelA pathway for up-regulation of cytokine expression in cardiomyocytes. *J Biol Chem.* 2010; 285:11596–606. [PubMed: 20145242]
47. Dey N, Sinha M, Gupta S, et al. Caspase-1/ASC inflammasome-mediated activation of IL-1beta-ROS-NF-kappaB pathway for control of *Trypanosoma cruzi* replication and survival is dispensable in NLRP3-/- macrophages. *PLoS One.* 2014; 9:e111539. [PubMed: 25372293]
48. Johndrow C, Nelson R, Tanowitz H, Weiss LM, Nagajyothi F. *Trypanosoma cruzi* infection results in an increase in intracellular cholesterol. *Microbes Infect.* 2014; 16:337–44. [PubMed: 24486184]
49. Nagajyothi F, Weiss LM, Zhao D, et al. High fat diet modulates *Trypanosoma cruzi* infection associated myocarditis. *PLoS Negl Trop Dis.* 2014; 8:e3118. [PubMed: 25275627]
50. Williams-Blangero S, Criscione CD, VandeBerg JL, et al. Host genetics and population structure effects on parasitic disease. *Philos Trans R Soc Lond B Biol Sci.* 2012; 367:887–94. [PubMed: 22312056]
51. Wen JJ, Zago MP, Nuñez S, Gupta S, Burgos FN, Garg NJ. Serum proteomic signature of human chagasic patients for the identification of novel potential protein biomarkers of disease. *Mol Cell Proteomics.* 2012; 11:435–52. [PubMed: 22543060]
52. Goldenberg RC, Jelicks LA, Fortes FS, et al. Bone marrow cell therapy ameliorates and reverses chagasic cardiomyopathy in a mouse model. *J Infect Dis.* 2008; 197:544–7. [PubMed: 18237267]
53. Parikh PP, Minning TA, Nguyen V, et al. A semantic problem solving environment for integrative parasite research: identification of intervention targets for *Trypanosoma cruzi*. *PLoS Negl Trop Dis.* 2012; 6:e1458. [PubMed: 22272365]
54. Carbajal-de-la-Fuente AL, Yadón ZE. A scientometric evaluation of the Chagas disease implementation research programme of the PAHO and TDR. *PLoS Negl Trop Dis.* 2013; 7:e2445. [PubMed: 24244761]
55. Kropf SP, Azevedo N, Ferreira LO. Biomedical research and public health in Brazil: the case of Chagas' disease (1909–50). *Soc Hist Med.* 2003; 16:111–29. [PubMed: 14598820]
56. Cantey PT, Stramer SL, Townsend RL, et al. The United States *Trypanosoma cruzi* Infection Study: evidence for vector-borne transmission of the parasite that causes Chagas disease among United States blood donors. *Transfusion.* 2012; 52:1922–30. [PubMed: 22404755]
57. Bern C, Kjos S, Yabsley MJ, Montgomery SP. *Trypanosoma cruzi* and Chagas' disease in the United States. *Clin Microbiol Rev.* 2011; 24:655–81. [PubMed: 21976603]
58. Gascon J, Bern C, Pinazo MJ. Chagas disease in Spain, the United States and other non-endemic countries. *Acta Trop.* 2010; 115:22–7. [PubMed: 19646412]
59. Click Lambert R, Kolivras KN, Resler LM, Brewster CC, Paulson SL. The potential for emergence of Chagas disease in the United States. *Geospat Health.* 2008; 2:227–39. [PubMed: 18686271]

60. Coura JR, Viñas PA. Chagas disease: a new worldwide challenge. *Nature*. 2010; 465:S6–7. [PubMed: 20571554]
61. Bern C, Montgomery SP. An estimate of the burden of Chagas disease in the United States. *Clin Infect Dis*. 2009; 49:e52–4. [PubMed: 19640226]
62. World Health Organization. Chagas disease (American trypanosomiasis). Jul 23. 2015 Available at: <http://www.who.int/mediacentre/factsheets/fs340/en/>. Accessed
63. Urbina JA. Recent clinical trials for the etiological treatment of chronic Chagas disease: advances, challenges and perspectives. *J Eukaryot Microbiol*. 2015; 62:149–56. [PubMed: 25284065]
64. Lannes-Vieira J, de Araujo-Jorge TC, Soeiro MN, Gadelha P, Corrêa-Oliveira R. The centennial of the discovery of Chagas disease: facing the current challenges. *PLoS Negl Trop Dis*. 2010; 4:e645. [PubMed: 20614014]
65. Tarleton RL, Reithinger R, Urbina JA, Kitron U, Gürtler RE. The challenges of Chagas disease—grim outlook or glimmer of hope. *PLoS Med*. 2007; 4:e332. [PubMed: 18162039]
66. National Heart, Lung, and Blood Institute. [Accessed August 1, 2015] The NHLBI Mission Statement. 2014. Available at: <http://www.nhlbi.nih.gov/about/org/mission>
67. Mensah GA, Kiley J, Mockrin SC, et al. National Heart, Lung, and Blood Institute Strategic Visioning: setting an agenda together for the NHLBI of 2025. *Am J Public Health*. 2015; 105:e25–8. [PubMed: 25723452]

FIGURE 1. Migration routes from Latin America and estimation of the total number of infected individuals in non-endemic countries

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