Neglected Diseases

The Challenges of Chagas Disease— Grim Outlook or Glimmer of Hope?

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Through its impact on worker productivity, premature disability, and death, Chagas disease accounts for 670,000 disability-adjusted life years per annum [1]. This makes it the most important parasitic disease of the Americas. It is both a disease of poverty (Figures 1 and 2) and, like other neglected tropical diseases, also "poverty promoting" [2]. Traditionally confined to Latin America, Chagas disease is becoming an important health issue in the United States and Europe. First, due to the continuous influx of immigrants from disease-endemic countries in Latin America, a proportion of whom are infected with *Trypanosoma cruzi*, an increasing number of infected subjects are seen in clinical practice, whether, for example, through routine screening of US blood and organ banks [3] or physicians' offices in Europe [4]. The appearance of *T. cruzi* in US blood banks led to the implementation of the first Food and Drug Administration–approved diagnostic blood screening test for Chagas disease earlier this year [5]. Second, an increasing number of autochthonous Chagas disease cases have been reported in the US [6,7], which may mirror the increased reporting of *T. cruzi* infection in domestic animals and wildlife. Recognizing that Chagas disease can no longer be considered an "exotic" disease in the US, the American Society of Tropical Medicine and Hygiene held a clinical course in Chagas disease prior to its 2007 annual meeting (http://www.astmh.org/meetings/premeeting.cfm#clinical).

Despite estimates of up to 15 million existing cases and 50,000–200,000 new infections per year, funding for research, prevention, and control has been limited, and therapeutic options remain unsatisfactory. Consequently, several editorials and perspectives have recently drawn attention to Chagas disease and *T. cruzi* [8–10]. While these papers highlighted the impact of this disease on public health in the Americas, and rightly pointed out that major achievements have been made in its control, they failed to emphasize several key challenges that are currently undermining these achievements and that must be urgently addressed in order to move to the next stage: ensuring the long-term and sustainable control of this devastating disease.

Etiology, Distribution, and Clinical Manifestations

Chagas disease (also known as American trypanosomiasis) is named for the Brazilian physician Carlos Chagas, who discovered the disease exactly a century ago and published its first description in 1909. It is caused by the protozoan parasite *T. cruzi* and is found in wildlife, domestic animals, and humans throughout much of rural as well as peri-urban areas of Mexico, Central America, and South America. In the US *T. cruzi* has been reported in dogs and a range of

The Neglected Diseases section focuses attention either on a specific disease or describes a novel strategy for approaching neglected health issues in general.

wild animals (e.g., raccoons and opossums), with human cases being relatively rare [6,7]. *T. cruzi* is mainly transmitted through blood-feeding triatomine bugs, but can also occur congenitally [7,11], through blood transfusion [12] or organ transplantation [13], and through the ingestion of contaminated food or fluids [14]. The complex life cycle involves different parasite life stages in both vector and host, all highly adapted to their respective environments, which maximizes transmission potential and/or host immune evasion and, hence, long-term parasite survival (http://www.dpd.cdc.gov/dpdx/HTML/TrypanosomiasisAmerican.htm#Life%20Cycle).

Most infected people do not know that they have become infected, as—in the disease's acute stage—the symptoms are benign (e.g., fever, swollen lymph glands, and, occasionally, an inflammatory reaction at the biting site or a swollen eye) or very rare (severe myocarditis or meningoencephalitis) [15]. Symptoms of acute infection may last up to a few weeks or months, and parasites may be found in the blood during this stage. Infections then remain largely asymptomatic (with few or no parasites found in the circulation), often for years or even decades, until up to 30% of patients develop chronic Chagas disease, i.e., cardiac or gastrointestinal complications, which if left untreated are severely debilitating

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Figure 1. Chagas Disease Is Closely Linked to Poverty and Socioeconomic Development, and Poor Housing In Particular
Example of a typical household environment in Chagas disease–endemic areas: mud-and-thatch house with a front veranda (in the background) and storage area (in the front), located in the dry Chaco forest around Amamá village, northern Argentina.

and in many cases, fatal [15]. Chagas cardiomyopathy, which may result in cardiac arrhythmias, apical aneurysm, congestive heart failure, thromboembolism, and sudden cardiac death (Figures 3 and 4), is the most common form of cardiomyopathy in South and Central America and the leading cause of cardiovascular death in disease-endemic areas [16]. In people with suppressed immune systems (e.g., due to HIV/AIDS or chemotherapy), Chagas disease can reactivate with abundant parasites found in the blood and tissues. Because of its potentially long asymptomatic phase, however, Chagas disease is often considered a "silent killer" [9], which is one of several reasons why it fails to attract media attention.

Grim Outlook 1: The Challenge of Vector Control

Tools to manage Chagas disease are numerous but are severely limited with regard to crucial aspects of prevention, detection, and treatment. Current vector control methods and strategies have significant limitations, diagnostics are variable and of unknown reliability, drugs for treatment are inadequate, and vaccines are nonexistent. Yet some bright spots exist, such as the decrease in transmission that has been achieved through control of insect vectors and screening of blood and blood products.

The "Southern Cone" initiative [17] has knocked down transmission rates dramatically in the southern tier of South America and is credited with interrupting vector-borne transmission via *Triatoma infestans* in Uruguay, Chile, and Brazil, primarily through insecticidal spraying of houses. However, elimination of *T. infestans* (one of the program's stated objectives) has not been achieved in the core of its distribution throughout the hyperendemic Gran Chaco region spanning northern Argentina, Paraguay, and Bolivia. Success may even be more difficult elsewhere in Latin America where there are many different vector species, each with distinct feeding and infestation behaviors, while in some endemic

countries, notably Mexico, no control programs for this disease have ever been established. Among the many problems with exclusive reliance on insecticides is that prevention of re-infestation of houses by the insect vectors requires repeated spraying, which also promotes the development of insecticidal resistance—an outcome that is already documented in Argentina [18] and is increasingly detected in Bolivia. There are alternative insecticides, but their use is accompanied by added problems of higher costs or increased toxicity.

The decentralization of health services in many endemic countries combined with declining funding for control efforts has transferred the burden of control to provinces or local communities that are ill-equipped to supply these services. Even if vector control were better coordinated and fully funded, eradication of either the many domestic vector species or the parasites is not feasible for this zoonosis. Potentially, improvements in housing could permanently reduce vectorial transmission. However, at a minimum cost of US$200 to more than US$2,000 per house [19], such improvements will have to await significant economic development in endemic areas or specific investments for housing improvements on the order of US$10 billion.

Grim Outlook 2: The Challenge of Chemotherapies and Vaccines

The current chemotherapies for *T. cruzi* infection and Chagas disease have many shortcomings, as do those in drug discovery and development. The available compounds for treatment, benznidazole (Rochagan, Roche Pharmaceuticals) and nifurtimox (Lampit, Bayer HealthCare), both have severe side effects, require long courses of treatment, and exhibit variable efficacy [20]. At present, the World Health Organization and other sources indicate that these drugs are active only in the acute and short-term (up to a few years) chronic phase (http://www.who.int/tdr/diseases/chagas/direction.htm). A number of studies now provide reason to

question this recommendation [21–27]. Although some of
these studies were non-controlled and used cure parameters
that may be debatable because of the absence of a diagnostic
gold standard (see below), they have been remarkably
consistent in showing moderate to significant efficacy in long-
term chronic infections. Thus, whilst waiting for the results
of, for example, the BENEFIT trial (http://clinicaltrials.
gov/ct/show/NCT00123916?order=1) evaluating the efficacy
of benznidazole in chronic Chagas disease patients (expected
to be completed in 2011), and unless or until better drugs are
available, benznidazole and nifurtimox should be more widely
used, based on the published evidence that such compounds
may reduce the parasite burden and moderate disease
progression in all stages of the disease [21–28]. It would
therefore be ethically questionable to restrict the drugs'
use to only patients with a defined duration of (acute and
short-term chronic) infection, as currently recommended.
However, the decision to treat chronic patients with these
drugs should be made on a case-by-case basis, only after
thorough clinical assessment and with continuous monitoring
of potential side effects.

Academic and other noncommercial drug discovery efforts
have yielded an increasing number of targets and new drug
candidates, but surprisingly few of these promising leads have
moved beyond the discovery/candidate stage. This stalemate
is due in part to limited funding for further research and
development, but even with drugs that have been available
for more than 25 years, such as benznidazole, definitive
preclinical evidence of cure in animal models is strikingly
absent. A recent report from the Wellcome Trust–supported
Pharmaceutical Research and Development Policy Project
concluded that there is increasing industrial interest and
progress in drug development for neglected diseases
[29]—but this is certainly not the case for Chagas disease.
Indeed, promising compounds such as Schering-Plough's
posaconazole have yet to be further pursued as anti–*T. cruzi*
drugs, despite extensive and promising preclinical data [20].

The success of drug treatment in arresting disease
progression in subjects who have been infected for more than
20 years [21,22], coupled with a wealth of other data, has
recently prompted a welcome shift toward studying Chagas
disease as a problem of parasite persistence, rather than
primarily as a problem of an inappropriate or imbalanced
immune response [30]. This shift has also generated more
interest in vaccines as a vehicle for control or treatment. Even
so, vaccine development for *T. cruzi* infection has had a very
slow start and remains nonexistent as a strategy for control
or prevention. There are substantial potential problems with
vaccines for Chagas disease, not the least of which include
how one would test a conventional prophylactic vaccine for an
infectious illness that is rarely detected until years or decades
after the initial infection. However, given the cost-effective
nature of vaccines and potential innovative applications (e.g.,
in transmission blocking or as therapeutics), more research
is warranted, and vaccines should be included in the overall
long-term strategy for control, prevention, and treatment of
T. cruzi infection.

Key Needs and Opportunities: Diagnostics and Integrated Vector Control
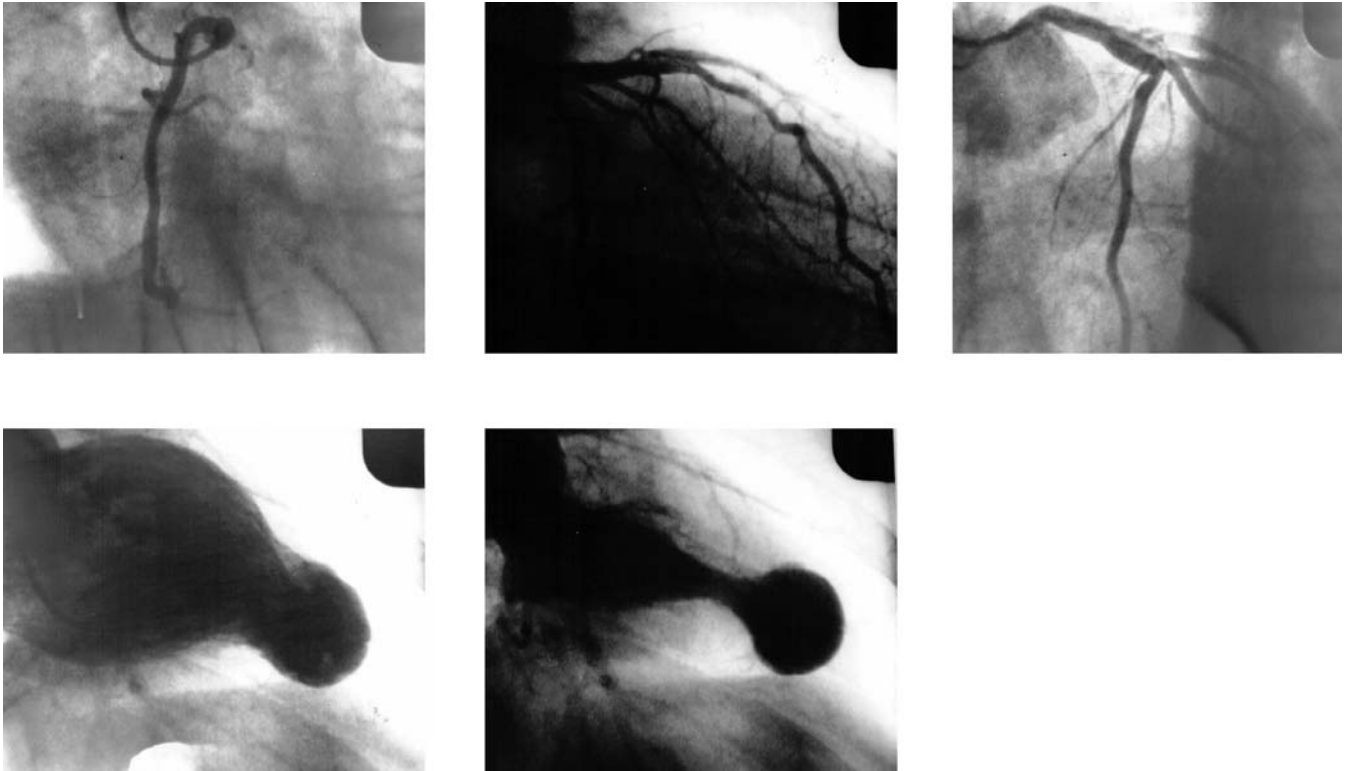
One of the key issues concerning Chagas disease is that of
diagnosis. Without effective diagnostics, infected individuals

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Figure 2. Interior of House Showing the Type of Wall Construction
Often Found in Households in Many Endemic Areas
Cracks in walls are commonly found, inhabited by insects, as evidenced
by the insect feces on wall and wall hangings.

cannot be identified and thus treated, and the effectiveness
of treatment cannot be efficiently assessed. Moreover, the
effectiveness of any control campaign, whether targeted
at insect vectors, blocking of transmission, or vaccination
of individuals, cannot be measured without competent
diagnostics. Transmission via blood transfusion or tissue
transplantation has been a point of concern for many years
in Latin America but has only come to the fore in the US and
Europe as the number of immigrants unknowingly carrying
T. cruzi has increased. Most current serological tests, whether
developed in-house or purchased commercially, employ
crude antigen preparations from inappropriate parasite life-
cycle stages (i.e., epimastigotes—which are present in the
insect vector but not in mammalian hosts). Development
of tests using one or more recombinant proteins/peptides
may be an improvement, but even these tests often provide
inconsistent and/or unreliable results [31–33]. The absence
of a true gold standard (i.e., a method to consistently detect
the presence of parasites in those individuals with *T. cruzi*
infection) makes evaluation of the sensitivity of serological
tests difficult. It is standard practice to use test sera that
are positive on multiple other serological tests to assess the
sensitivity of new tests, proving that any new test is no worse,
but not necessarily any better, than existing ones. However,
it is well documented that individuals with confirmed
infection are typed as inconclusive or negative on multiple
existing serological tests [34–36]. The design of tests to
detect these inconclusive or "conventional seronegative"
subjects has not been a priority. Likewise, the development of
technologies that can more rapidly assess treatment efficacy,
diagnose congenital infections, or determine the impact of
transmission control methods has been slow. Fortunately, the
development of sensitive, accurate, and practical diagnostic
methods is a highly tractable problem, given an appropriate
level of investment and interest. The development of highly
sensitive and specific diagnostic field and laboratory tools
to determine active infection is a crucial requirement for
moving the entire field forward in the research, clinical, and
public health arenas.

Figure 3. Cineventriculogram of a 49-Year-Old Male with Chagas Heart Disease
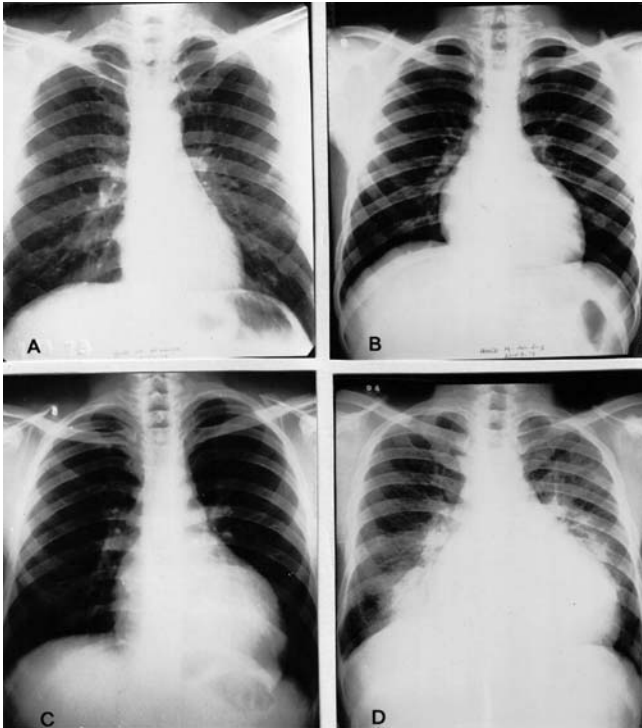The picture shows the apical aneurysm (sacular) with normal coronary arteries.

Although vector management has been the foundation of the overall strategy for prevention of *T. cruzi* infection, this area is also ripe for improvements. Despite the long-held promises of vector suppression through residual spraying with pyrethroid insecticides, current procedures often fail to eliminate triatomine bugs, especially in semiarid rural areas and in peridomestic habitats [37]. The lack of simple, sensitive tools for early detection of low-density populations of triatomine bugs that reappear after insecticide spraying undermines the effectiveness of control and elimination programs. Traditional high-risk settings require integrated control programs that are tailored to local environmental and sociocultural characteristics and employ a long-term perspective. The bust-and-boom cycles of the recent past, largely dependent on available funding, demonstrate that the effectiveness of Chagas disease vector control as currently practiced is limited.

On the other hand, progress in related research can help counter these shortcomings in vector control strategies. Our understanding of the eco-epidemiology of infection has significantly improved in recent years, especially with the application of geospatial analytical tools. These advances have allowed the development of infection and disease transmission models [38] as well as the more targeted planning of prevention and control strategies coupled with continued surveillance (e.g., identification of so-called transmission "hotspots" or loci of bug re-infestation) [39]. Several tools to prevent infection and to control (peri-) domestic bug populations have been evaluated, including insecticide-treated bed-nets [40] and dog collars [41], and optimum insecticide doses in peridomestic habitats. These tools have been shown to effectively reduce the contact of humans or reservoir dogs with the triatomine vector of *T. cruzi*. Bed-nets and collars would become particularly attractive options if they were used in an integrated approach aimed at controlling other vector-borne diseases such as malaria and leishmaniasis, respectively. The key issue is whether or not these new tools can be applied successfully at geographic scales ranging from individual villages to entire regions where current methods are not sufficient for the desired objective (control versus elimination).

Glimmer of Hope

The problems of Chagas disease are many, but they are not insurmountable. There are numerous *partial* solutions already at hand that, if used in a coordinated manner, and with consideration of the unique characteristics of endemic areas (e.g., rural underdevelopment, poverty, lack of adequate housing, and increasingly decentralized health services), could have a significant impact. The entities that will fund and coordinate such an integrated effort remain to be identified, but clearly the involvement of the public sector is essential. Better diagnostics, drugs, and improved approaches to vector control programs will require more and better research, sharper focus, and greater rigor on the part of the research community. In addition, contributions from governments, the private sector, and nongovernmental organizations will be needed to establish the infrastructure for testing drugs and control methods as well as the platforms to develop and implement effective and affordable diagnostic tests. Fortunately, the research community has provided the majority of potential drug, vaccine, and diagnostic candidates

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Figure 4. Chest X-Ray of 4 Different Patients with Chagas Heart Disease
A: normal; B: mild cardiomegaly; C: moderate cardiomegaly; D: severe cardiomegaly with pulmonary congestion.

and, via the sequencing of the *T. cruzi* genome and proteomes [42,43], has presented multiple leads for drug targets and diagnostic/vaccine candidates. However, neither for-profit nor nonprofit companies have taken on the challenges of developing these leads further. Effective scientific, philanthropic, and political leadership and forward-thinking coordination of a community effort in this realm, at both local and regional levels, is badly needed if we want to make significant inroads into this devastating disease. Ultimately, the success of such efforts will be heavily dependent on the long-term stability and prospects for economical, societal, and political development in the Americas. ∎

Supporting Information

Acknowledgements

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