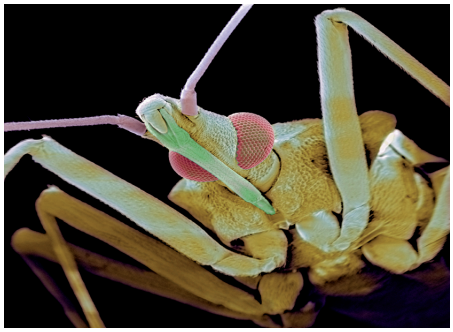


VOLKER STEGER/SPL

Triatomine bug: the vector for *T Cruzi*

Eliminating Chagas disease: challenges and a roadmap

Millions of people in Central and South America are affected by Chagas disease. **Richard Reithinger and colleagues** explain the difficulties of elimination and suggest a strategy

In 2007, the World Health Organization announced a renewed strategy to eliminate Chagas disease in the Americas by 2010.[1] The intention was "to answer key questions about the treatment and control of Chagas disease, and to coordinate global efforts towards the prevention of transmission through a new Global Network for Chagas Elimination."[1] The announcement was welcome because it put the spotlight on Chagas disease, which has been overshadowed by other priorities, such as HIV and malaria, in recent years. However, two years later, WHO has yet to produce a clear strategy for elimination and we are unaware of any new operational activities to eliminate the disease. Too many challenges remain.

Scale of the problem

Chagas disease is both a disease of poverty and, like other neglected tropical diseases, poverty promoting.[2] An estimated 10-20 million people live with the condition and it is responsible for a burden of 670 000 disability adjusted life years,[3] making it the most important parasitic disease in the Americas.

The disease is caused by the protozoan parasite *Trypanosoma cruzi*,[4] which is transmitted through the faeces of blood feeding triatomine bugs; trypomastigotes in the faeces contaminate the wound or enter through mucosal surfaces.[5] It can also be transmitted by blood transfusions, organ donations, through the placenta, or by eating contaminated food. Most people do not know that they have become infected with *T cruzi* because the acute symptoms tend to be unspecific or benign (fever, swollen lymph glands, inflammation at the biting site or a swollen eye, and, rarely, severe myocarditis or meningoencephalitis). In mammals, *T cruzi* must invade host cells in order to replicate. It ultimately destroys these cells, stimulating tissue inflammation and releasing infective extracellular trypanomastigote forms, which propagate the infection through the body.

After the acute phase, which lasts a few weeks or months, the infection is generally well controlled by the host immune response. Nonetheless, parasites continue to cycle in and out of host cells but are only transiently in the bloodstream and thus difficult to detect, with symptoms not evident for years or even decades. Eventually, however, up to 40% of infected people develop chronic Chagas disease. This chronic stage of the disease is characterised by cardiac or gastrointestinal complications, which if left untreated are severely debilitating and often fatal. Indeed, Chagas disease is the most common cause of cardiomyopathy in South and Central America and the leading cause of cardiovascular death in disease endemic areas.[6] In people who have suppressed immune systems (because of HIV infection or chemotherapy, for example), Chagas disease can reactivate with abundant parasites found in the blood and tissues commonly leading to severe meningoencephalitis, which is fatal if untreated.

T cruzi is found in triatomine bugs, wildlife, domestic animals, and humans throughout much of rural and peri-urban areas of North, Central, and South America (figure). Although autochthonous vector borne human cases are scarce in the United States,[7 8] and non-existent in Canada and Europe, *T cruzi* has been detected in triatomine bugs, dogs, and wildlife in the US[7 9] and is increasingly detected in the US, Canada, and Europe among immigrants or tourists from Latin America.[10-12] After the detection of a number of cases in blood donors,[13] the US FDA approved a screening assay for blood donors in 2007.

Large regional control programmes have reduced the incidence of Chagas disease in the southern tier of South America and some other regions in the last decade.[14] Vector borne transmission has been reduced or even halted, mainly through residual spraying of domestic and peridomestic household structures with insecticide, and blood donations are routinely screened for *T cruzi*. Uruguay, Chile, and Brazil are currently declared free of *T cruzi* transmission by the main vector *Triatoma infestans*.

Challenges of elimination

Eradication of Chagas disease is impossible because of the zoonotic characteristics of the *T cruzi* transmission cycle.[4] Control of the disease is also hampered by several operational and policy challenges and knowledge gaps.[15] For example, increasing insecticide resistance of bugs and the recolonisation of households by bugs after insecticide treatment are reducing the impact of vector control; no consensus exists on whether benznidazole and nifurtimox is the best treatment for adult chronic infection (the most prevalent presentation) and the drugs have been in short supply[16 17]; there is no agreed standard for diagnosis, with laboratories using a combination of serological tests that may give inconclusive or false negative results[18]; and there is no vaccine to prevent Chagas disease.

Whether the intention of WHO is to stop the development of Chagas disease in populations at risk or halt vector borne transmission of *T cruzi* to humans is not clear. Too many challenges persist to expect successful elimination of Chagas disease by 2010. Resurgence of vector borne transmission after apparent elimination, as witnessed in Argentina during the 1990s, shows that without proper planning or emphasis on consolidation and sustainability, successes may be short lived. *T cruzi* transmission still persists in many regions of Latin America (two large outbreaks of orally transmitted *T cruzi* were reported in Venezuela in the past 15 months) and has entered peri-urban areas in some places, such as Arequipa, Peru.[19] A realistic, sustainable strategy to interrupt the human transmission of *T cruzi* should be developed and a strategy to treat and manage the millions of currently infected individuals needs to be established.

The first step is to get a good understanding of the extent of the disease. WHO stated "current estimates suggest that less than 8 million people remain infected,"[1] but with no recent nationwide surveys of *T cruzi* infection (except in Brazil and Chile), the estimate is suspect. No up to date data on the burden and distribution of Chagas disease exist for Mexico, Peru, Colombia, Costa Rica, and much of the Amazonian region. Indeed, as recently as 2005 only 361 cases of the disease were reported by the Mexican Ministry of Health,[20] yet focal studies in rural areas showed seroprevalence of up to

30% and up to 82.5% of patients with congestive heart failure testing seropositive for *T cruzi*.[21]

Road map

Given these challenges and gaps,[15] how should we develop a comprehensive strategy for eliminating Chagas disease? Below we outline what we believe should be the main components.

Better monitoring and estimation of true burden of disease

Cost constraints mean that a disease specific regional surveillance system is probably not feasible. Instead there should be advocacy to integrate Chagas disease into a country's health monitoring information system or other disease surveillance programmes (malaria, dengue, or tuberculosis). Additionally, representative surveys (similar to the malaria indicator surveys developed under Roll Back Malaria's monitoring and evaluation reference group)[22] should be carried out regularly to estimate domestic infestation, the incidence of Chagas disease, prevalence of coinfections, disability associated with the disease, and population knowledge of the disease's diagnosis, treatment, prevention, and control. Both surveillance and surveys would contribute to getting more accurate data to estimate disease burden as well as to monitor and evaluate the effect of a putative elimination strategy.

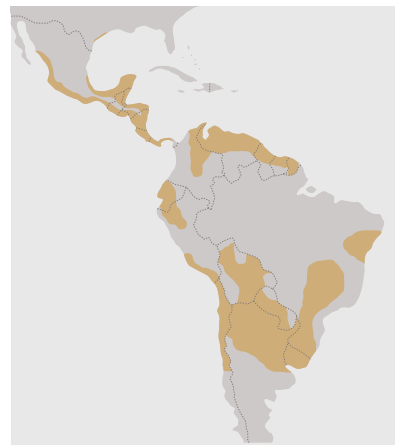
We also need a better understanding of the burden of Chagas disease. Clarification should be obtained about the nature and origin of the measures used to calculate disability adjusted life years (prevalence of disease, age at death and mortality, duration of disease) and how the disability weight for Chagas disease was computed. Similarly, clarification should be obtained about how cases are detected and reported at national and regional level (active or passive case reporting; mandatory notification, etc). These efforts should be complemented by sensitivity and specificity analyses to determine more robust estimates of the disease burden as well as to show how different measures to calculate the disability adjusted life years attributed to Chagas disease affect current national and regional estimates.

Standard diagnostic procedures

The substantial number of inconclusive diagnoses[18] shows we need a valid and accepted standard diagnostic procedure. The available diagnostic procedures (which include enzyme linked immunosorbent assays, immunofluorescence antibody tests, radioimmune precipitation assays, and polymerase chain reaction based assays) vary in sensitivity, particularly if not properly standardised. The absence of a standard method for detecting *T cruzi* not only makes it impossible to determine the true impact of Chagas disease but also makes the development of new diagnostics extremely challenging.

A WHO consultative meeting last year highlighted the need for substantial investment in the development of new and better diagnostics, using the increased understanding of the genetic makeup and diversity of *T cruzi* and new technologies for improved, rapid, and cost effective diagnostics.[23] A uniform set of diagnostic standards obtained from the entire geographic range of *T cruzi* and incorporating confirmed but problematic samples (positive on some current tests but negative on others) must be established. Though for many years WHO and the Pan American Health Organisation have supported external validation of samples in selected reference laboratories, it is unclear how many local laboratories use that service. A first step in reaching this goal may be the recent decision to develop and provide a panel of reference samples to laboratories in endemic countries[24] and to conduct complex multicentre trials comparing a range of diagnostic tests.

In addition, there should be a recommendation, internationally recognised and endorsed, on uniform case descriptions of Chagas disease, algorithms for diagnosis, and standardised approaches to estimate case numbers through active and passive detection in endemic settings. Although many endemic countries have standard definitions for clinical disease, definitions, algorithms, and protocols for confirmatory, laboratory diagnosis may differ within and between countries. Thus, in Argentina diagnosis of chronic Chagas disease is based on the results of two independent, standardised serological tests,[25] but which tests and their protocol is not specified. El Salvador requires two confirmatory serological tests after an initial positive result,[26] but again the nature of the tests is not specified.



Chagas disease is endemic in all Latin American countries. Brown shading shows the main areas where vector borne transmission of *T cruzi* to humans occurs

Effective treatment strategy

The elimination of Chagas disease implies the effective treatment of millions of people already infected with *T cruzi* in the American continent and now in non-endemic areas as well. This is a massive undertaking that obviously requires identification of the patients as well as the availability of safe, effective, and affordable drugs. Currently available drugs (nifurtimox and benznidazole)[27] are generally accepted to be effective in treating acute and early chronic infections in children younger than 15 years but their efficacy and availability is not uniform through all endemic regions. Treatment efficacy in longer term chronic infections, however, remains controversial,[16 17] as are the criteria (conventional serology and direct methods to evaluate parasitaemia) currently used to assess drug efficacy. This, coupled with the common occurrence of side effects, leads many doctors to view the risk:benefit ratio of such treatments as unfavourable. Despite important advances in preclinical studies,[27] no new drugs have entered clinical trials in more than a decade. In the meantime a strategy to manage these patients is urgently required and should be part of any elimination efforts.

Increased spraying coverage and monitoring of insecticide resistance

Any elimination strategy will rely on spraying of households with insecticides as its main approach for vector control. Spraying needs to be maintained in those areas where it is currently implemented and expanded to cover more endemic areas in order to significantly affect *T cruzi* transmission. Monitoring and reporting of insecticide resistance are required, given the recent reports of insecticide resistance in triatomine bugs. A range of insecticides may need to be used rather than just the currently used pyrethroid insecticides to prevent resistance from developing and expanding. Unfortunately, there are few non-toxic, affordable alternatives to pyrethroid insecticides that are effective against triatomine bugs. Other approaches for vector control have proved effective in preventing infection in humans, such as insecticide treated bednets[28] or preventing bugs from feeding on animal reservoirs by using insecticide treated dog collars.[29] However, these interventions have yet to be tested operationally on a large scale and their cost effectiveness needs to be assessed.

Coordination

Any elimination effort will have to be implemented in the context of increasingly decentralised health services,[30] the loss of operational

capacity and of technical knowledge about vector control. Many government disease control programmes have lost qualified staff through retirement and are overburdened by other communicable diseases. There is a shortage of public health officers and entomologists trained to design and manage vector control programmes or use the information technology and geographical information systems that are now commonly used in modern vector control. To counterbalance one of the negative impacts of decentralisation, more trained local staff are urgently needed.

Finally, for any elimination strategy to be successful, coordination between national, regional, and international policymakers, public health professionals, and academics is essential.

WHO's efforts to highlight Chagas disease as an important public health issue and to suppress this devastating, poverty promoting disease should be fully supported. However, to successfully accomplish this bold undertaking, a realistic, sustainable strategy to interrupt the human transmission of *T cruzi* is prerequisite.

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ANSWERS TO ENDGAMES, p 1085

For long answers use advanced search at bmj.com and enter question details

PICTURE QUIZ

4 year old boy with recurrent wheeze and chest infections

1 Oesophageal pH monitoring, which is used widely as an index of oesophageal acid exposure—it measures the frequency and duration of episodes of acid reflux.
2 Multiple episodes of gastro-oesophageal reflux—113 reflux episodes in 20 hours and 52 minutes (5.3 per hour) (table). Some of the reflux episodes were prolonged, and the longest reflux event lasted for 31 minutes. Overall, pH was <4 for 9.7% of the study, which is indicative of severe gastro-oesophageal reflux.
3 The limitations of the pH study are that it does not detect non-acidic reflux episodes, it cannot diagnose pulmonary aspiration, it gives no indication of the volume of refluxate, the location of the probe must be confirmed radiographically, it cannot detect anatomical abnormalities (such as hiatus hernia or stricture), and it does not provide an objective measure of inflammation.
4 Medical treatment should be the first option. Infants respond favourably to changes in positioning, and some small infants respond well to thickening of feeds. Gastric acidity can be reduced by a histamine (H2) antagonist (such as ranitidine) or a proton pump inhibitor (such as omeprazole or lansoprazole). A prokinetic agent, such as domperidone or low dose erythromycin, can be used to accelerate emptying of the stomach. Surgical treatment is only indicated when adequate medical treatment fails.

STATISTICAL QUESTION

Incidence and prevalence

c

CASE REPORT

A taxi driver with type 2 diabetes

1 Ascertain what outcomes he hopes for from the consultation, and try to integrate these with your desired outcomes. Reinforce the importance of good management of chronic disease. Offer referrals to structured education and dietetic services.
2 Published evidence supports efforts to lower glycated haemoglobin to 7.0%, and this is reflected by some, but not all, of the national and international guidelines. Evidence for pursuing a more aggressive target of <7.0% is limited, and the two recently published large scale randomised controlled trials studying such an approach gave conflicting results.
3 The patient drives for a living, so for safety reasons he must take extra care to avoid hypoglycaemia. He is currently taking a sulphonylurea (gliclazide), but it might be better to change him to a drug that is less likely to cause hypoglycaemia, such as a thiazolidinedione or a dipeptidylpeptidase-4 (DDPIV) inhibitor. Because he has recently had several hypoglycaemic episodes, he should stop driving until glycaemic control without hypoglycaemia can be achieved.