

Chagas disease

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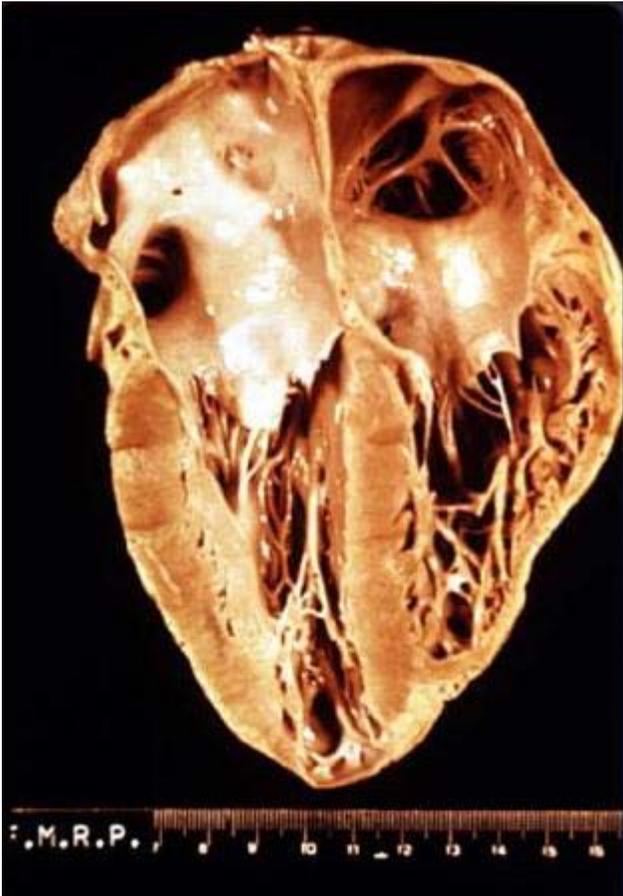
Chagas disease ([ⓘ] /ˈʃɑːɡəs/, Portuguese: [ˈʃaxɐ]; Portuguese: *doença de Chagas*, Spanish: *enfermedad de Chagas-Mazza*, *mal de Chagas* in both languages; also called **American trypanosomiasis**) is a [tropical parasitic disease](#) caused by the [flagellate protozoan](#) *Trypanosoma cruzi*. *T. cruzi* is commonly transmitted to humans and other mammals by an insect [vector](#), the [blood-sucking](#) insects of the subfamily [Triatominae](#) (family [Reduviidae](#)) most commonly species belonging to the *Triatoma*, *Rhodnius*, and *Panstrongylus* genera.^[1] The disease may also be spread through [blood transfusion](#) and [organ transplantation](#), ingestion of food contaminated with [parasites](#), and [from a mother to her fetus](#).^[2]

The symptoms of Chagas disease vary over the course of an infection. In the early, acute stage, symptoms are mild and usually produce no more than local swelling at the site of infection. The initial acute phase is responsive to [antiparasitic](#) treatments, with 60–90% cure rates. After 4–8 weeks, individuals with active infections enter the chronic phase of Chagas disease that is asymptomatic for 60–80% of chronically infected individuals through their lifetime. The antiparasitic treatments also appear to delay or prevent the development of disease symptoms during the chronic phase of the disease, but 20–40% of chronically infected individuals will still eventually develop life-threatening heart and digestive system disorders. The currently available antiparasitic treatments for Chagas disease are [benznidazole](#) and [nifurtimox](#), which can cause temporary side effects in many patients including skin disorders, brain toxicity, and digestive system irritation.^{[3][4][5]}

Chagas disease is contracted primarily in the Americas, particularly in poor, rural areas of [Mexico](#), Central America, and South America; very rarely, the disease has originated in the Southern United States. The insects that spread the disease are known by various local names, including *vinchuca* in Argentina, Bolivia, Chile and Paraguay, *barbeiro* (the [barber](#)) in Brazil, *pito* in Colombia, *chinche* in Central America, *chipó* in Venezuela, *chupança*, *chinchorro*, and "the kissing bug". It is estimated that as many as 8 to 11 million people in Mexico, Central America, and South America have Chagas disease, most of whom do not know they are infected. Large-scale population movements from

rural to urban areas of Latin America and to other regions of the world have increased the geographic distribution of Chagas disease, and cases have been noted in many countries, particularly in Europe.^{[4][6]} Control strategies have mostly focused on eliminating the triatomine insect vector and preventing transmission from other sources.^[1]

Signs and symptoms



 Gross anatomy of a heart that has been damaged by chronic Chagas disease - see also: [Chagas heart, radiology](#)

The human disease occurs in two stages: an [acute](#) stage, which occurs shortly after an initial [infection](#), and a [chronic](#) stage that develops over many years.

The **acute phase lasts for the first few weeks or months of infection. It usually occurs unnoticed because it is symptom-free or exhibits only mild symptoms that are not unique to Chagas disease. These can include fever, fatigue, body aches, headache, rash, loss of appetite, diarrhea, and vomiting. The signs on physical examination can include mild enlargement of the liver or spleen, swollen glands, and local swelling (a chagoma) where the parasite entered the body. The most recognized marker of acute Chagas disease is called Romaña's sign, which includes swelling of the eyelids on the side of the face near**

the bite wound or where the bug feces were deposited or accidentally rubbed into the eye. Rarely, young children, or adults may die from the acute disease due to severe inflammation/infection of the heart muscle (myocarditis) or brain (meningoencephalitis).^[7] The acute phase also can be severe in people with weakened immune systems.^[1]

If **symptoms** develop during the acute phase, they usually **resolve spontaneously within three to eight weeks** in approximately 90% of individuals.^{[3][4]} Although the symptoms resolve, even with treatment the **infection persists and enters a chronic phase**. Of **individuals with chronic Chagas disease**, 60–80% will never develop symptoms (called *indeterminate* chronic Chagas disease), while the remaining 20–40% will **develop life-threatening heart and/or digestive disorders during their lifetime** (called *determinate* chronic Chagas disease). In 10% of individuals, the disease progresses directly from the acute form to a symptomatic clinical form of chronic Chagas disease.^{[3][4]}

The symptomatic (determinate) **chronic stage affects the nervous system, digestive system and heart**. About two-thirds of people with chronic symptoms have cardiac damage, including dilated cardiomyopathy, which causes heart rhythm abnormalities and may result in sudden death. About one-third of patients go on to develop digestive system damage, resulting in dilation of the digestive tract (megacolon and megaesophagus), accompanied by severe weight loss. Swallowing difficulties (secondary achalasia) may be the first symptom of digestive disturbances and may lead to malnutrition.^[2] 20% to 50% of individuals with intestinal involvement also exhibit cardiac involvement.^[2] Up to 10% of chronically infected individuals develop neuritis that results in altered tendon reflexes and sensory impairment. Isolated cases exhibit central nervous system involvement, including dementia, confusion, chronic encephalopathy and sensitivity and motor deficits.^[8]

The **clinical manifestations of Chagas disease are due to cell death in the target tissues that occurs during the infective cycle, by sequentially inducing an inflammatory response, cellular lesions, and fibrosis**. For example, intracellular amastigotes destroy the intramural neurons of the autonomic nervous system in the intestine and heart, leading to megaintestine and heart aneurysms, respectively. If left untreated, Chagas disease can be fatal, in most cases due to heart muscle damage.^[2]

Transmission



Rhodnius prolixus is the principal vector in Colombia, Venezuela, Guatemala, Honduras and some parts of Nicaragua and El Salvador.

In Chagas-endemic areas, the main mode of transmission is through [an insect vector](#) called a triatomine bug.^[1] A triatomine becomes infected with *T. cruzi* by feeding on the blood of an infected person or animal. During the day, triatomines hide in crevices in the walls and roofs. The bugs emerge at night, when the inhabitants are sleeping. Because they tend to feed on people's faces, triatomine bugs are also known as "kissing bugs". After they bite and ingest blood, they defecate on the person. Triatomines pass *T. cruzi* parasites (called [trypomastigotes](#)) in feces left near the site of the bite wound. Scratching the site of the bite causes the trypomastigotes to enter the host through the wound, or through intact [mucous membranes](#), such as the [conjunctiva](#). Once inside the host, the trypomastigotes invade cells, where they differentiate into intracellular [amastigotes](#). The amastigotes multiply by [binary fission](#) and differentiate into trypomastigotes, which are then released into the bloodstream. This cycle is repeated in each newly infected cell. Replication resumes only when the parasites enter another cell or are ingested by another vector.^[1] (See also: [Life cycle and transmission of *T. cruzi*](#))

Dense vegetation (such as that of tropical [rainforests](#)) and urban habitats are not ideal for the establishment of the human transmission cycle. However, in regions where the [sylvatic habitat](#) and its fauna are thinned by economic exploitation and human habitation, such as in newly [deforested](#) areas, [piassava palm](#) culture areas, and some parts of the [Amazon](#) region, a human transmission cycle may develop as the insects search for new food sources.^[9]

T. cruzi can also be transmitted through [blood transfusions](#). With the exception of blood derivatives (such as fractionated [antibodies](#)), all blood components are infective. The parasite remains viable at 4°C for at least 18 days or up to 250 days when kept at room temperature. It is unclear whether *T. cruzi* can be transmitted through frozen-thawed blood components.^[10]

Other modes of transmission include [organ transplantation](#), through [breast milk](#),^[11] and by accidental laboratory exposure. Chagas disease can also be spread congenitally (from a pregnant woman to her baby) through the [placenta](#), and accounts for approximately 13% of stillborn deaths in parts of Brazil.^[12]

Oral transmission is an unusual route of infection, but has been described. In 1991, farm workers in the state of [Paraíba](#), Brazil, were infected by eating contaminated food; transmission has also occurred via contaminated [açai palm](#) fruit juice and [sugar cane juice](#).^{[13][14][15]} A 2007 outbreak in 103 Venezuelan school children was attributed to contaminated [guava](#) juice.^[16]

Chagas Disease is a growing problem in Europe, because the majority of cases with chronic infection are asymptomatic and because of migration from Latin America.^[6]

Diagnosis



Photomicrograph of [Giemsa](#)-stained *Trypanosoma cruzi* ([CDC](#))

The presence of *T. cruzi* is diagnostic of Chagas disease. It can be detected by [microscopic](#) examination of fresh [anticoagulated](#) blood, or its [buffy coat](#), for motile parasites; or by preparation of thin and thick blood smears stained with [Giemsa](#), for direct visualization of [parasites](#). Microscopically, *T. cruzi* can be confused with [Trypanosoma rangeli](#), which is not known to be [pathogenic](#) in humans. Isolation of *T. cruzi* can occur by inoculation into [mice](#), by culture in specialized media (for example, NNN, LIT); and by [xenodiagnosis](#),^[17] where uninfected [Reduviidae](#) bugs are fed on the patient's blood, and their gut contents examined for parasites.^[2]

Various [immunoassays](#) for *T. cruzi* are available and can be used to distinguish among [strains](#) ([zymodemes](#) of *T. cruzi* with divergent pathogenicities). These tests include: detecting [complement fixation](#), indirect [hemagglutination](#), indirect [fluorescence](#) assays, [radioimmunoassays](#), and [ELISA](#). Alternatively, diagnosis and strain identification can be made using [polymerase chain reaction](#) (PCR).^[2]

Prevention



Awareness and prevention campaign poster in [Cayenne, French Guiana](#), 2008

There is currently **no vaccine against Chagas disease**^[18] and prevention is generally focused on fighting the [vector](#) *Triatoma* by using sprays and paints containing [insecticides](#) (synthetic [pyrethroids](#)), and improving housing and sanitary conditions in rural areas.^[19] For urban dwellers, spending vacations and [camping](#) out in the wilderness

or sleeping at hostels or mud houses in endemic areas can be dangerous; a [mosquito net](#) is recommended. Some stepstones of vector control include:

- A yeast trap can be used for monitoring infestations of certain species of triatomine bugs (*Triatoma sordida*, *Triatoma brasiliensis*, *Triatoma pseudomaculata*, and *Panstrongylus megistus*).^[20]
- Promising results were gained with the treatment of vector habitats with the fungus *Beauveria bassiana*.^[21]
- Targeting the [symbionts](#) of [Triatominae](#) through [paratransgenesis](#) can be done.^[22]

A number of potential vaccines are currently being tested. Vaccination with *Trypanosoma rangeli* has produced positive results in animal models.^[23] More recently, the potential of DNA vaccines for [immunotherapy](#) of acute and chronic Chagas disease is being tested by several research groups.^[24]

Blood transfusion was formerly the second-most common mode of transmission for Chagas disease, but the development and implementation of [blood bank screening tests](#) has dramatically reduced this risk in the last decade. [Blood donations](#) in all endemic Latin American countries undergo Chagas screening, and testing is expanding in countries, such as France, Spain and the United States, that have significant or growing populations of immigrants from endemic areas.^{[25][26]} In Spain, donors are evaluated with a questionnaire to identify individuals at risk of Chagas exposure for screening tests.^[26] The US FDA has approved two Chagas tests, including one approved in April 2010, and has published guidelines that recommend testing of all donated blood and tissue products.^{[26][27]} While these tests are not required in U.S., an estimated 75–90% of the blood supply is currently tested for Chagas, including all units collected by the [American Red Cross](#), which accounts for 40% of the U.S. blood supply.^{[27][28]} The Chagas Biovigilance Network reports current incidents of Chagas-positive blood products in the United States, as reported by labs using the screening test approved by the FDA in 2007.^[29]

Management

There are two approaches to treating Chagas disease, [antiparasitic](#) treatment, to kill the parasite; and symptomatic treatment, to manage the symptoms and signs of infection.

Medication

Antiparasitic treatment is most effective early in the course of infection, but is not limited to cases in the acute phase. Drugs of choice include [azole](#) or [nitro](#) derivatives, such as [benznidazole](#)^[30] or [nifurtimox](#). Both agents are limited in their capacity to effect parasitologic cure (a complete elimination of *T. cruzi* from the body), especially in chronically infected patients, and resistance to these drugs has been reported.^[31] Studies suggest antiparasitic treatment leads to parasitological cure in about 60–85% of adults and more than 90% of infants treated in the first year of acute phase Chagas disease. Children (aged six to 12 years) with chronic disease have a cure rate of about 60% with

benznidazole. While the rate of cure declines the longer an adult has been infected with Chagas, treatment with benznidazole has been shown to slow the onset of heart disease in adults with chronic Chagas infections.^{[2][4]}

Treatment of chronic infection in women prior to or during pregnancy does not appear to reduce the probability the disease will be passed on to the infant. Likewise, it is unclear whether [prophylactic](#) treatment of chronic infection is beneficial in persons who will undergo immunosuppression (for example, organ transplant recipients) or in persons who are already immunosuppressed (for example, those with HIV infection).^[2]

Complications

In the chronic stage, treatment involves managing the clinical manifestations of the disease. For example, [pacemakers](#) and medications for irregular heartbeats, such as the anti-arrhythmia drug [amiodarone](#), may be life saving for some patients with chronic cardiac disease,^[32] while surgery may be required for megaintestine. The disease cannot be cured in this phase, however. Chronic heart disease caused by Chagas disease is now a common reason for [heart transplantation](#) surgery. Until recently, however, Chagas disease was considered a [contraindication](#) for the procedure, since the heart damage could recur as the parasite was expected to seize the opportunity provided by the [immunosuppression](#) that follows surgery.^[33] It was noted that survival rates in Chagas patients could be significantly improved by using lower dosages of the immunosuppressant drug [ciclosporin](#). Recently, direct [stem cell therapy](#) of the heart muscle using [bone marrow cell transplantation](#) has been shown to dramatically reduce risks of heart failure in Chagas patients.^[34]

Epidemiology



 Chagas in Latin America (A: [Endemic](#) zones)

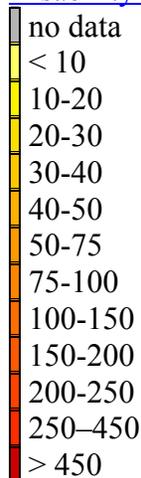
Chagas disease affects eight to 10 million people living in endemic Latin American countries, with an additional 300,000–400,000 living in nonendemic countries, including Spain and the United States. An estimated 41,200 new cases occur annually in endemic

countries, and 14,400 infants are born with congenital Chagas disease annually. About 20,000 deaths are attributed to it each year.^{[2][4]}

The disease is present in 18 countries on the American continents, ranging from the southern United States to northern [Argentina](#).^[1] Chagas exists in two different ecological zones. In the [Southern Cone](#) region, the main vector lives in and around human homes. In Central America and Mexico, the main vector species lives both inside dwellings and in uninhabited areas. In both zones, Chagas occurs almost exclusively in rural areas, where triatomines breed and feed on the over 150 species from 24 families of domestic and wild mammals, as well as humans, that are the [natural reservoirs](#) of *T. cruzi*.^[35] Although Triatominae bugs feed on them, birds appear to be immune to infection and therefore are not considered to be a *T. cruzi* reservoir. Even when colonies of insects are eradicated from a house and surrounding domestic animal shelters, they can re-emerge from plants or animals that are part of the ancient, [sylvatic](#) (referring to wild animals) infection cycle. This is especially likely in zones with mixed open savannah, with clumps of trees interspersed by human habitation.^[36]



[Disability-adjusted life year](#) for Chagas disease per 100,000 inhabitants in 2004^[37]



The primary wildlife reservoirs for *Trypanosoma cruzi* in the United States include [opossums](#), [raccoons](#), [armadillos](#), [squirrels](#), [woodrats](#) and [mice](#).^[38] Opossums are particularly important as reservoirs, because the parasite can complete its life cycle in the anal glands of the animal without having to re-enter the insect vector.^[38] Recorded prevalence of the disease in opossums in the U.S. ranges from 8.3%^[38] to 37.5%.^[39] Studies on raccoons in the Southeast have yielded infection rates ranging from 47%^[40] to as low as 15.5%.^[38] Armadillo prevalence studies have been described in Louisiana, and range from a low of 1.1%^[39] to 28.8%.^[41] Additionally, small rodents, including squirrels,

mice and rats, are important in the sylvatic transmission cycle because of their importance as bloodmeal sources for the insect vectors. A Texas study revealed 17.3% percent *T. cruzi* prevalence in 75 specimens representing four separate small rodent species.^[42]

Chronic Chagas disease remains a major health problem in many Latin American countries, despite the effectiveness of hygienic and preventive measures, such as eliminating the transmitting insects. However, several landmarks have been achieved in the fight against it in Latin America, including a reduction by 72% of the incidence of human infection in children and young adults in the countries of the [Southern Cone Initiative](#), and at least three countries ([Uruguay](#), in 1997, and [Chile](#), in 1999, and Brazil in 2006) have been certified free of vectorial and transfusional transmission.^{[2][43][44]} In Argentina, vectorial transmission has been interrupted in 13 of the 19 endemic provinces,^[43] and major progress toward this goal has also been made in both Paraguay and Bolivia.

Screening of donated blood, blood components, and solid organ donors, as well as donors of cells, tissues and cell and tissue products for *T. cruzi* is mandated in all Chagas-endemic countries and has been implemented.^[45] Approximately 300,000 infected people live in the United States, which is likely the result of immigration from Latin American countries.^[46] With increased population movements, the possibility of transmission by blood transfusion became more substantial in the United States. Transfusion blood and tissue products are now actively screened in the U.S., thus addressing and minimizing this risk.^[47]

History



 Carlos Chagas, in his laboratory at the Instituto Oswaldo Cruz.

The disease was named after the [Brazilian](#) physician and [infectologist](#) [Carlos Chagas](#), who first described it in 1909,^{[48][49][50][51]} but the disease was not seen as a major [public health](#) problem in humans until the 1960s (the outbreak of Chagas disease in Brazil in the 1920s went widely ignored^[52]). He discovered that the intestines of Triatomidae (now

[Reduviidae: Triatominae](#)) harbored a flagellate protozoan, a new species of the *Trypanosoma* genus, and was able to prove experimentally that it could be transmitted to [marmoset](#) monkeys that were bitten by the infected bug. Later studies showed [squirrel monkeys](#) were also vulnerable to infection.^[53]

Chagas named the pathogenic parasite as *Trypanosoma cruzi*^[48] and later that year as *Schizotrypanum cruzi*,^[50] both honoring [Oswaldo Cruz](#), the noted Brazilian physician and [epidemiologist](#) who successfully fought epidemics of [yellow fever](#), [smallpox](#), and [bubonic plague](#) in [Rio de Janeiro](#) and other cities in the beginning of the 20th century. Chagas was also the first to unknowingly discover and illustrate the parasitic fungal genus *Pneumocystis*, later famously linked to PCP (*Pneumocystis pneumonia* in AIDS victims).^[49] Confusion between the two pathogens' life-cycles led him to briefly recognize his genus *Schizotrypanum*, but following the description of *Pneumocystis* by others as an independent genus, Chagas returned to the use of the name *Trypanosoma cruzi*.

In [Argentina](#), the disease is known as *mal de Chagas-Mazza*, in honor of [Salvador Mazza](#), the [Argentine](#) physician who in 1926 began investigating the disease and over the years became the principal researcher of this disease in the country.^[54] Mazza produced the first scientific confirmation of the existence of *Trypanosoma cruzi* in Argentina in 1927, eventually leading to support from local and European medical schools and Argentine government policy makers.^[55]

It has been hypothesized that [Charles Darwin](#) might have suffered from Chagas disease as a result of a bite of the so-called great black bug of the [Pampas](#) (*vinchuca*) (see [Charles Darwin's illness](#)). The episode was reported by Darwin in his diaries of [the Voyage of the Beagle](#) as occurring in March 1835 to the east of the [Andes](#) near [Mendoza](#). Darwin was young and generally in good health, though six months previously he had been ill for a month near [Valparaiso](#), but in 1837, almost a year after he returned to England, he began to suffer intermittently from a strange group of [symptoms](#), becoming incapacitated for much of the rest of his life. Attempts to test Darwin's remains at the [Westminster Abbey](#) by using modern [PCR](#) techniques were met with a refusal by the Abbey's [curator](#).^[56]

Research

Several experimental treatments have shown promise in animal models. These include inhibitors of [oxidosqualenecyclase](#) and [squalene synthase](#),^{[57][58]} [cysteine protease](#) inhibitors,^{[57][59]} [dermaseptins](#) collected from frogs in the genus *Phyllomedusa* (*P. oreades* and *P. distincta*),^[60] the [sesquiterpene lactone](#) dehydroleucodine (DhL), which affects the growth of cultured [epimastigote](#)-phase *Trypanosoma cruzi*,^[61] inhibitors of [purine](#) uptake,^[57] and inhibitors of enzymes involved in [trypanothione](#) metabolism.^[62] Hopefully, new drug targets may be revealed following the sequencing of the *T. cruzi* [genome](#).^[63] A 2004 *in vitro* study suggests components of [green tea](#) ([catechins](#)) may be effective against *T. cruzi*.^[64]

Folding@Home

The distributed Computing program [Folding@home is studying Chagas Disease](#). They are applying ligand-based methods to Chagas disease in collaboration with the SPARK project (UCSF) and the McKerrow Lab (UCSF). Everyone can help by donating unused CPU/GPU resources. ^{[[citation needed](#)]}

See also

- [Drugs for Neglected Diseases Initiative](#)
- [Chagas: Time to Treat campaign](#)
- [Association for the Promotion of Independent Disease Control in Developing Countries](#)

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