The epidemiology of Chagas disease in the Americas

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Summary

Chagas disease is a complex parasitic zoonosis that still threatens public health across the Americas. Initiatives to control *Trypanosoma cruzi* transmission *via* blood transfusion and non-native triatomine-bug vectors have yielded crucial advances; native vectors, however, actively bridge wild and domestic/peri-domestic transmission cycles throughout the region, and tens of thousands of people become infected each year. Oral-transmission outbreaks, urbanisation, and vertical transmission are additional/emerging issues calling for innovative strategic thinking. While critical for advocacy and sustained public health action, assessing Chagas disease burden remains difficult; the often-asymptomatic nature of *T. cruzi* infection, healthcare access limitations, pervasive underreporting, and other methodological hurdles inherent to reliably measuring incidence, prevalence, and disease progression all contribute to the difficulty. Whether and how parasite, vector, and host genetic makeups affect transmission dynamics and epidemiology is also unclear. Continued high-quality research and long-term, adaptive strategies combining vector control surveillance with enhanced case detection and integral patient care remain critical to effectively address the ethical and societal challenge of Chagas disease control.

This is the first in a Series of five papers about Chagas Disease. All papers in the Series are available at https://www.thelancet.com/series/chagasdisease.

Keywords: Chagas disease; *Trypanosoma cruzi*; Transmission; Disease burden; Control

Introduction

Chagas disease, caused by the multi-host zoonotic parasite *Trypanosoma cruzi*, was first identified in 1909 and has been endemic in the Americas for over nine millennia.[1] Many factors contribute to shaping the complex epidemiology of the disease, including environmental conditions, host and vector biology, human behaviour, socioeconomic/political determinants, control programmes, and possibly parasite genetics.[2–4] With seven genetically distinct "discrete typing units" (DTUs TcI to TcVI plus TcBat), *T. cruzi* is a remarkably diverse protozoan.[3] In recent decades, declining vector-borne transmission (due mainly to vector-control efforts and improved housing) and increasing prevalence in previously non-endemic settings (due mainly to international and rural-to-urban migration) have substantially modified the disease landscape. These changes pose new challenges for understanding transmission dynamics and disease burden and for devising effective control and prevention strategies.[5]

Chagas disease primarily spreads to humans *via* blood-sucking true bugs of the subfamily Triatominae

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(Hemiptera: Reduviidae).[6] Of about 160 known species across five tribes and 18 genera, the most important vectors are several American species of *Triatoma*, *Rhodnius*, and *Panstrongylus*.[6–8] *T. cruzi* transmission cycles also involve over 150 domestic, synanthropic (i.e., living in close association with humans), and wild mammalian host species in at least eight orders—Didelphimorphia (opossums), Cingulata (armadillos), Pilosa (sloths, anteaters), Rodentia (rodents), Chiroptera (bats), Carnivora (e.g., dogs, cats), Artiodactyla (e.g., goats, pigs, donkeys), and Primates (monkeys and humans).[9–11] Transmission occurs primarily when a vector feeds on the blood of a susceptible mammal and releases faeces and/or urine containing infective forms of the parasite, which then enter the host through skin lesions or mucous membranes.[2–6,12] Human-vector contact is more frequent, and transmission more likely, when triatomine bugs stably infest houses.[6] Other transmission routes include blood transfusion, organ transplantation, consumption of infected food or beverages, and vertical transmission from mother to foetus; predation of infected triatomines may be a relevant infection route among non-human mammals (Table 1).[2,12–24]

Despite the large reductions in transmission by house-infesting vectors, Chagas disease remains endemic across continental Latin America, with about 75 million people living at risk of infection.[27,28] Estimates by the World Health Organization/Pan American Health Organization (WHO/PAHO) suggest that, between the early 1990s and 2010, prevalence fell from ~18 to 6–8 million infected people, and incidence fell from ~200,000 to ~40,000 new cases per year.[28,29]

Estimates from the Global Burden of Disease (GBD) study,[30] however, differ substantially for both past prevalence (~7.3 million infected people in 1990; ~6.7 million in 2010) and recent incidence (~186,000 new cases in 2010; ~240,000 in 1990).[30] While these discrepancies highlight the hurdles inherent to getting robust estimates of key epidemiological parameters and merit detailed scrutiny, steady progress in Chagas disease control is nevertheless undeniable.[25,31] Such progress owes mainly to national and regional public-health initiatives fostering vector control and blood- and organ-donor screening,[32] likely with contributions from secular trends of housing-quality improvement and the rural exodus,[33,34] and has shifted focus towards vertical and oral transmission.[18,25]

Crucially, however, the vast majority of new infections (likely >90%) go undiagnosed, and an estimated 70% of infected individuals are unaware of their condition.[2,13,35] While early detection of *T. cruzi* infection significantly increases the odds of treatment success,[36,37] only about 1% of those infected receive specific aetiological treatment (for which two drugs, benznidazole and nifurtimox, are available) in the Americas.[38,39] If left untreated, Chagas disease—and in particular acute oral infections and chronic cardiac and digestive symptomatic forms—is associated with considerable morbidity, mortality, and overall burden.[13,25] The wide gap between diagnostic/therapeutic needs and resources arises from a combination of (i) the asymptomatic/oligosymptomatic (i.e., without or with few signs or symptoms) nature of most infections and (ii) healthcare-related issues, including limited Chagas disease awareness among health staff and policymakers, under-resourced primary-care systems,

Route	Details and likelihood of infection
Vector-borne	In Chagas disease-endemic areas from the southern USA to northern Argentina and Chile, *Trypanosoma cruzi* transmission is primarily mediated by vectors.[6,25] Large-scale insecticide-spraying campaigns have drastically reduced transmission by non-native populations of *Triatoma infestans*, *T. dimidiata*, and *Rhodnius prolixus*.[25] However, house-invading and house-infesting native populations of these three 'primary' and dozens of other 'secondary' vector species maintain transmission in rural and peri-urban communities throughout the Americas.[25] Even though the underlying mechanism is rather inefficient,[26] this persistent, geographically-widespread transmission mediated by native vectors still causes thousands of new infections per year and remains the primary driver of incidence.[25] Most new vector-borne infections (up to ~95%) are asymptomatic/oligosymptomatic and remain undiagnosed and unreported.[13]
Vertical	Vertical transmission is the main source of new infections in non-endemic countries/territories and in urban settings where vectors are rare or absent.[14,25] Frequency estimates, however, are sparse and heterogeneous. The probability of transmission from infected mother to child usually ranges between ~1-2 and ~5–6%, and may be higher in endemic than in non-endemic countries.[15,16] High parasite loads likely increase, and anti-*T. cruzi* treatment of infected childbearing-aged women likely reduces, the odds of vertical transmission; the roles of maternal immune status, twin pregnancy, or parasite strains/genotypes should be better elucidated.[14,25] Not all endemic countries consistently implement screening programs.[17,25]
Oral	Oral transmission probably helps maintain enzootic infection among non-human mammals.[18,19] It may also be a relevant source of human infections, with localised outbreaks and isolated cases reported with increasing frequency from several countries.[18,20,25] Contamination of food or beverages by infected vectors (or, more rarely, opossums) is likely the main underlying mechanism, but consumption of infected mammals might also play a role.[20] High infectious loads often result in a more severe clinical picture, including more severe acute myocarditis, than what is usually seen in classical vector-borne transmission.[21] This conspicuous clinical picture, together with active contact-tracing during outbreaks, likely increases the fraction of incident cases that are diagnosed and reported.[25]
Transfusion	Transfusion-associated *T. cruzi* transmission was once a major issue, but nearly-universal donor screening in blood banks across all endemic countries has effectively brought it under control.[22,25] The risk of infection after transfusion of one unit of blood from an infected donor has been estimated at ~10–20% in endemic countries; recent evidence from non-endemic settings suggests that risk may be ~6–26% for platelets, but just ~0–4% for packed red blood cells, plasma, and cryoprecipitates.[23]
Organ transplantation	The risk of transmission associated with transplantation of an organ from an infected donor has been reported to vary between ~13 and ~75% in various cohorts and seems to be organ-specific, with transmission apparently less likely in kidney and liver recipients than in heart recipients.[24]

Table 1: Trypanosoma cruzi *transmission routes and probability of infection.*

inadequate availability of point-of-care testing and specific drugs, and low screening coverage.[25,40] Bridging this gap, which disproportionately affects underserved communities and social groups,[4,41] is vital for reducing the burden of Chagas disease and for enhancing patient health outcomes.[25]

In this series paper we review the current status of Chagas disease in the Americas. We focus primarily on *T. cruzi* transmission and spread, on the individual and societal burden associated with Chagas disease, and on the strategies used to alleviate such burden. Our aim is not only to provide an updated synthesis of current knowledge, but also to contribute to inform future research, interventions and policies. Other papers published in this Chagas disease series cover further relevant aspects including disease progression and severity,[55] the potential effects of climate change on vector-borne transmission,[56] diagnosis,[57] and recent developments in vaccines and therapeutics.[58]

Transmission of *Trypanosoma cruzi*, past and present

Vector-borne transmission

Chagas disease transmission dynamics involve complex interactions between *T. cruzi*, its insect vectors, and its mammalian hosts including humans (Fig. 1). Notably, however, many other components of the environment also play important roles in *T. cruzi* transmission. For example, climate/eco-regional patterns and human-mediated (passive) dispersal may dictate which vector and host species (co-)occur at coarse geographic scales;[59] land-use patterns (e.g., deforestation, urbanisation) may modulate landscape-scale vector abundance and infection or host-community composition;[60–62] and ecotope-scale vector abundance and infection often vary with, e.g., microhabitat structure (building materials, palm–crown complexity), microclimate, bloodmeal availability (including the blood of vertebrates that do not host *T. cruzi*, such as birds), human behaviour (e.g., insecticide use, husbandry of domestic animals), predation/pathogen pressure, or the bugs' microbiota.[62–67] We emphasise, then, that Fig. 1 (and similar figures found in some textbooks and papers) is a simplified depiction of the intricate network of trophic/ecological interactions that—further modulated by parasite, vector, and host genetics—ultimately underpin vector-mediated *T. cruzi* transmission.

A key historical event in the transition of *T. cruzi* from wildlife parasite to widespread human pathogen was the accidental introduction of a few highly synanthropic populations of *Triatoma infestans*, *T. dimidiata*, and *Rhodnius prolixus* beyond their native ranges.[29] These non-native triatomines heavily infested homes but did not spread back into wild habitats, and became known as 'primary', 'domestic', or 'strictly domiciliated' vectors. Non-native 'primary' vectors were successfully targeted by

large-scale insecticide-spraying campaigns (see below), but still persist in northern Colombia (*R. prolixus*), coastal Ecuador (*T. dimidiata*), and parts of Peru, Argentina, Paraguay and, to a lesser extent, Chile and Brazil (*T. infestans*).[25] Importantly, all 'primary' vector species are *native* to some subregion of Latin America: *T. infestans* to the dry Chaco and the Bolivian montane dry forests, *R. prolixus* to the Orinoco basin, and *T. dimidiata* to Mesoamerica-northern South America (Fig. 2).[6–8,68–72] These three and 140+ further native-American triatomine bug species maintain *T. cruzi* transmission cycles in highly diverse microhabitats (from underground to forest canopy) and ecoregions (from hyper-arid deserts to hyper-moist rainforests) over most of the Americas (Fig. 2).[6–8]

Many such native species also invade and infest houses and peridomestic structures in rural, periurban, and urban settings across the region (Fig. 2).[6–8,68–70] The prevention of recurrent/persistent *T. cruzi* transmission to humans by these native vectors is a critical standing challenge.[25] Strictly wild vector populations involved in enzootic transmission cycles are not targets for control, but, to the extent that they occasionally enter houses, should be the objects of surveillance.[68–73]

The distinction between 'native' and 'non-native' vector species—which, we note, can only be made after specifying a geographic unit (e.g., country or ecoregion) of reference—has major practical implications: simply put, non-native populations can be locally eliminated, whereas native vectors with widespread wild populations cannot.[68–70,73] Thus, the native/non-native dichotomy was central to the insecticide-based elimination of non-native *T. infestans* and *R. prolixus* from large swathes of, respectively, the Southern Cone and Mexico/Central America,[25,74,75] but more flexible/adaptive strategies—emphasising the long-term control-surveillance of native vectors and fully integrating case detection and patient care—will be required as the remaining non-native populations dwindle.[25,69,70] Critical to the design and operation of such sustainable strategies is the issue of shrinking vector- and case-detection probabilities.[73] First, the 'classical' pattern of spatially-clustered, heavy house infestations by a single non-native vector species is replaced by a pattern of recurrent house invasions and small infestation foci scattered over vast geographic areas and involving many, often little-known native species.[25,68,70] Second, primary-healthcare workers become less familiar with acute Chagas disease as new vector-borne infections, which are almost always asymptomatic or oligo-symptomatic,[13] become rarer, further lowering the chances of case detection.[73] As risk and incidence become less visible, policymakers may feel justified in diverting limited resources away from Chagas disease surveillance, which can only reduce visibility even further and may lead to a perverse, positive feedback loop undermining disease prevention.[68]
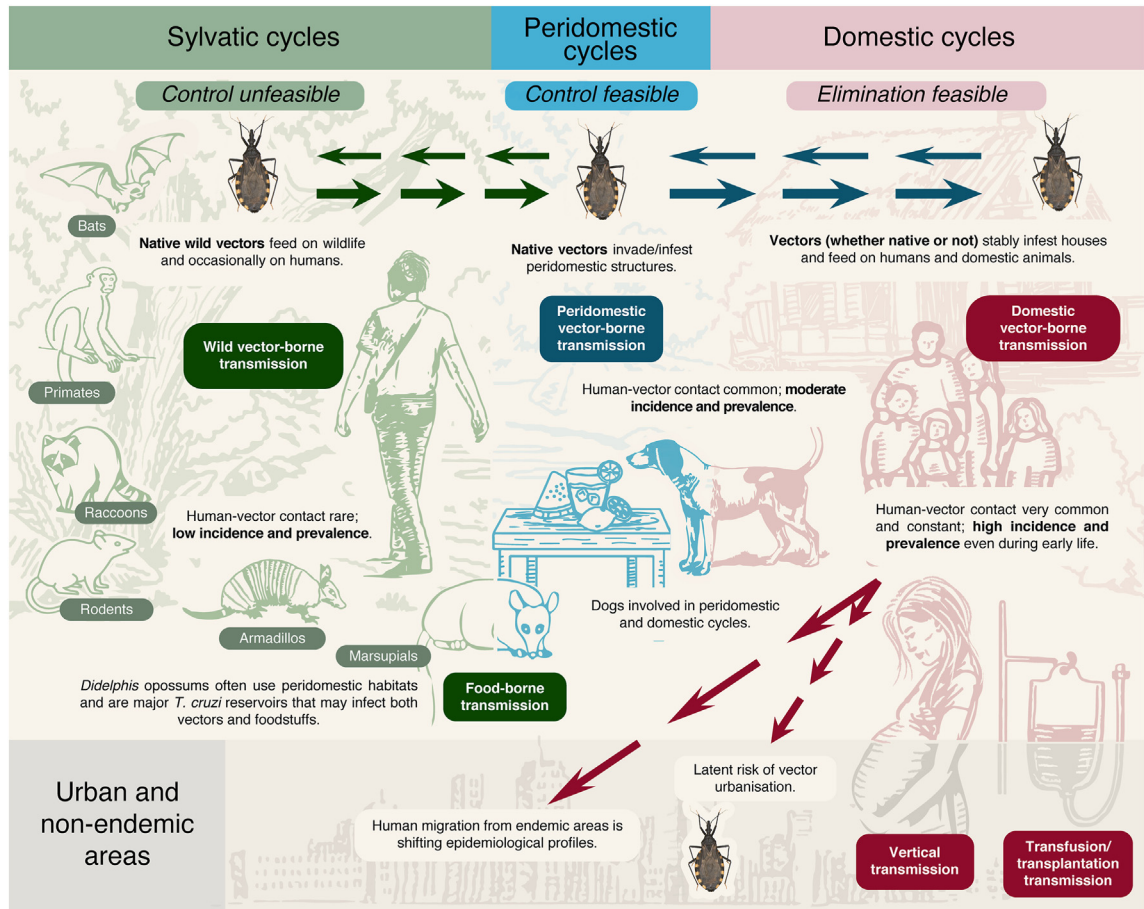
Fig. 1: Ecoepidemiology and transmission dynamics of Chagas disease in the Americas.

Vertical transmission

Vertical (mother-to-child) transmission of *T. cruzi* is the leading driver of Chagas disease incidence in vector-free non-endemic countries and in Latin American cities or territories where vector- and transfusion-mediated transmission are effectively under control.[76–79] In 2010, WHO/PAHO estimated that ~1.13 million women of childbearing age (15–44 y old) were infected with *T. cruzi,* leading to approximately 8700 new cases of congenital Chagas disease each year.[28] More recently, PAHO suggested that at least 15,000 cases occur annually in Latin America.[25,80]

Meta-analytic summaries of the average rate of vertical *T. cruzi* transmission (or 'risk', measured as the percent of infected children among those born to infected mothers) have ranged from ~4.7% (95% CI 3.9–5.6; studies published in 1975–2012) to ~2.0% (1.0–2.0; studies published in 2004–2019).[15,16] Transmission risk appears to vary widely among subregions, and may be higher in endemic (~5%) than in non-endemic countries (~3%).[15,78,81] A recent prospective, multicentric observational study illustrates inter-country

variation within Latin America.[82] Seropositive mothers (73.2% of which also tested positive by blood PCR) were enrolled in Mexico (*n* = 32), Honduras (*n* = 182), and Argentina (*n* = 136); while Argentina and Mexico reported vertical transmission rates of 6.6% (95% CI 3.1–12.2) and 6.3% (0.8–20.8), respectively, there were no confirmed congenital cases in Honduras.[82] The factors driving this variation in vertical-transmission risk remain overall poorly understood.[14] Higher maternal bloodstream parasite loads probably increase vertical-transmission risk, and risk may also be higher when previous pregnancies resulted in vertical transmission and when the mother's infection was itself congenital.[81,83–87] The evidence is weaker or inconclusive in the case of other putative transmission-risk drivers/modulators—including characteristics of mothers (e.g., age, parity, residence in urban *vs* rural areas, exposure to vectors, immune-effector levels), newborns (e.g., sex, number of siblings, birth order, immune effectors), and parasites (DTUs, strains, virulence factors)—, and further research is needed to clarify their effects and relative importance.[14,78,81]
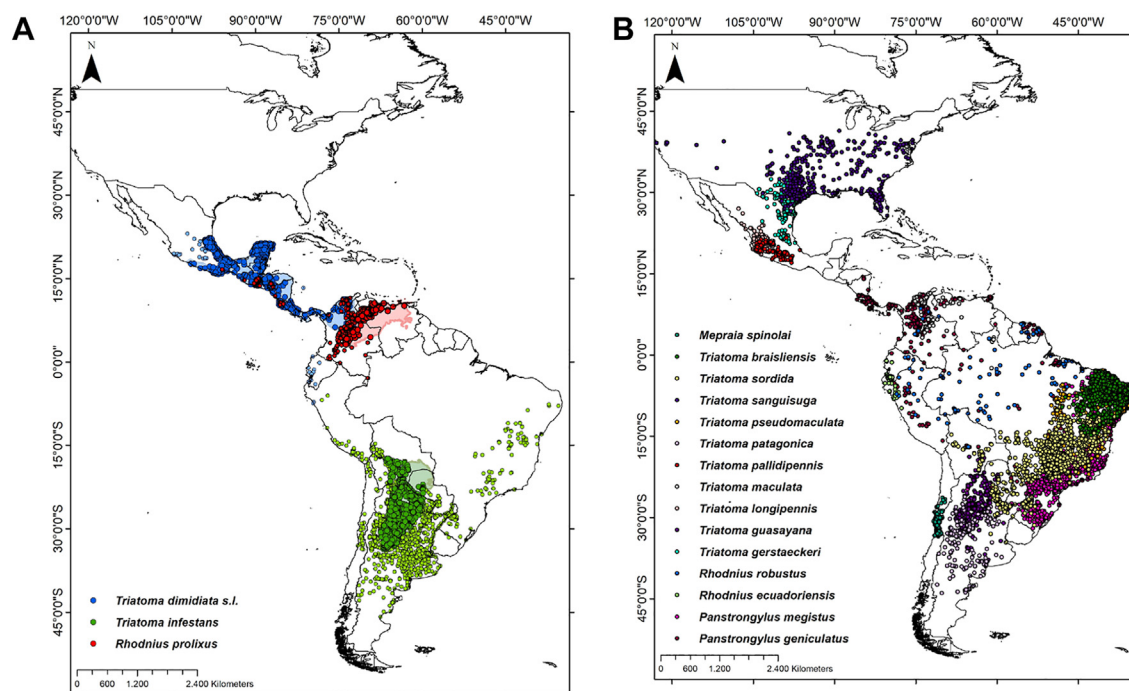
Fig. 2: Distribution of *Trypanosoma cruzi* vector species in the Americas. Main domiciliated vector species (Panel A): larger and darker points correspond to records within the ecoregion-level native range of each species (light-coloured shapes), and smaller and lighter points to records of non-native populations (some of which have already been eliminated).[7,25] Other important vector species (Panel B). Data sourced mainly from DataTri 2022.[71,72]

Crucially, mounting evidence suggests that treatment of infected childbearing-aged girls and women with specific anti-*T. cruzi* drugs reduces the odds of vertical transmission in subsequent pregnancies.[25,88–93] Furthermore, the early detection of congenital infections virtually guarantees treatment success, with cure rates close to 100%.[77,78] These findings have galvanised efforts towards expanding maternal and newborn Chagas disease screening, including the PAHO-led 'EMTCT plus Framework for Elimination of Mother-To-Child Transmission of HIV, Syphilis, Hepatitis B, and Chagas'—which advocates for the inclusion of *T. cruzi*-infection testing in routine ante/perinatal screening and seeks to (i) achieve 90% *T. cruzi*-screening coverage of pregnant women and children born to seropositive mothers, and (ii) provide treatment to 90% of seropositive women after delivery and infant breast-feeding.[80,94] Economic evaluations suggest that ante/perinatal screening for *T. cruzi* infection, with specific treatment offered when needed, would be clearly cost-effective in both endemic and non-endemic settings.[77,95] Routine screening, however, has yet to be widely implemented; substantial variation in diagnostic guidelines/algorithms across countries and territories reflects both technical/operational hurdles and a lack of expert consensus.[25,77,95] Universal screening of

childbearing-aged women born in (or to mothers from) endemic regions might hold the key to the primary prevention of congenital Chagas disease.[25,77,81]

Oral transmission
Oral transmission of *T. cruzi* is much more efficient than 'classical' (percutaneous) vector-borne transmission[96] and may represent the ancestral transmission route.[21,97–99] It is probably common among wild insectivorous/omnivorous mammals that eat infected triatomines, among carnivores that eat infected prey, and among didelphid opossums exposed to anal scent-gland secretions of infected conspecifics.[10,19,98,100] Similarly, transmission to humans may be the result of eating/drinking (i) raw or undercooked meat/organs/blood of infected mammals or, more frequently, (ii) food/beverages contaminated by infected vectors (or their faeces/urine) or by the scent-gland secretions of infected opossums.[20] Oral transmission of human Chagas disease has been documented in Colombia, Venezuela, Brazil, French Guiana, Ecuador, Bolivia, and Argentina, but probably occurs elsewhere too.[81,98,99,101–103] Foodborne transmission tends to yield spatial–temporal case-clusters or 'outbreaks' of acute Chagas disease involving people who shared an infected meal, although isolated cases have also been reported and many might

go undiagnosed.[101] There is no conclusive evidence about transmission of *T. cruzi* through breast-feeding—which should only be discontinued in acute or reactivated Chagas disease or if there is nipple bleeding.[104]

While outbreaks of foodborne Chagas disease were first reported in the late 1960s,[105] some recent, well-studied instances—such as the 2007 Caracas outbreak resulting in 103 infections among students and staff at a local school—have highlighted the importance of this transmission route.[106] An investigation of 49 outbreaks across South America up to 2019 identified 15 outbreaks associated with the consumption of açaí (*Euterpe* spp.) palm-fruit pulp—a staple food in the eastern Brazilian Amazon.[107] Sugar-cane juice, fruit juices (guava, mango, orange, or rose-apple), palm products (mainly from *Attalea* and *Oenocarpus* spp.), and even water and soup, have also been linked to outbreaks; the evidence, though, is often circumstantial, and in many outbreaks no specific source of infection was identified.[107] Genotyping of *T. cruzi* isolates from a small number of foodborne outbreaks revealed TcI in Colombia, Venezuela, French Guiana, and northern Brazil; TcII in southern Brazil; and TcIII and TcIV in the Brazilian Amazon.[101,102,106,108–111]

Foodborne *T. cruzi* infections are often more clinically patent, more severe, and more deadly than vector-borne infections; this has been linked to overall larger infectious loads, and may result in a particularly high per-case disease burden.[20] Importantly, increased disease severity and active contact tracing/testing—which usually ensue when oral transmission is suspected—both enhance the visibility of orally-transmitted acute infections, thus helping reduce underreporting. This is a sharp contrast to the often asymptomatic vector-borne infections.[25,107]

Although prevention of foodborne Chagas disease is still an open issue, current knowledge suggests that it will require considering distinct transmission scenarios in (mainly) urban *vs* rural settings.[111–116] Urban outbreaks may involve (i) infected vectors accidentally carried within fruit cargos from harvesting or distribution sites into nearby cities; (ii) local vector populations breeding in, e.g., urban parks, forest remnants, or human dwellings; or (iii) synanthropic opossums (that live in close association with humans and thrive in anthropic environments).[113–115] Contamination of commercially-distributed foodstuffs is of greater concern in urban than in rural settings. Rural outbreaks (and likely also isolated transmission events) are often linked to family- or community-based production of non-commercial food or beverages that become contaminated when vectors fall into (or infest) food-processing gear.[113,114] In both rural and urban settings, foodborne Chagas disease prevention and early case detection and management require strong inter-sectoral health education, promotion, and communication initiatives aimed at all stakeholders—food producers, distributors, vendors, and consumers; healthcare providers; public-health officials and decision-makers; and the general public.[25,96,112] Food-safety regulation is seen as key to preventing urban outbreaks linked to food retail, but rural transmission may be less sensitive to regulation. In rural settings, prevention should focus instead on creating the conditions for safer food production and management at the household level, including, e.g., insect-screening of food-processing premises/equipment and improved hygiene along the entire production process—from food handling, processing, and storing to the maintenance of food-related gear.[25,96,112,116]

Transfusion- and transplantation-mediated transmission

Transfusion-associated *T. cruzi* transmission caused tens of thousands of new infections per year up to the early 1990s.[117–119] Since then, nearly-universal donor screening in endemic countries has effectively brought it under control.[25,22,120] Screening is now mandatory in all countries where the parasite circulates naturally, including the USA.[12,25] However, the sheer amount of donations and transfusions, the often non-negligible prevalence of infection among donors, and the slightly suboptimal performance of screening tests, taken together, mean that mandatory screening likely misses a non-trivial number of infected donations. For example, WHO/PAHO estimates that ~93 per 10,000 (0.93%) blood donations made in Latin America in 2010 contained *T. cruzi*[28]; assuming that *all* donations were screened with a highly (99%) sensitive test, then ~930 infected donations yielded (false-)negative screening-test results, and hence were labelled as safe, per million blood donations. This suggests that *T. cruzi* infection likely went undetected in over 9000 of the ~9.9 million blood donations that, according to PAHO, were made in Chagas disease-endemic countries in 2017.[121] Although not all infected donations necessarily result in *T. cruzi* transmission (see Table 1), clinicians and public-health officials should keep in mind that sporadic transfusion-related infections likely occur each year across the Americas in spite of universal screening.[25,120]

According to WHO/PAHO estimates for 2010, the average prevalence of *T. cruzi* infection among blood donors (given here as number of positives per 10,000) in 17 Latin American countries ranged from 45 in Costa Rica to ~3000 in Argentina (median, 390; IQR 190–1340).[28] Prevalence was >2000 in Argentina, Paraguay, and Bolivia; >1000 in El Salvador and Guatemala; and relatively low (<200) in Costa Rica, Chile, Honduras, Brazil, and Ecuador.[28] Prevalence was intermediate (~350 per 10,000 donors) in Guyana by the late 2000s.[122] In the USA, recent estimates vary from 3.3 (ref. [12]) to 6.4 (ref. [123]), with much higher values reported for, e.g., Florida (~26), California (~12 overall but up to ~36 in the southern part of the state), and Texas (~15 per 10,000).[123–125] Data from Canada suggest a prevalence slightly above 3 per 10,000

donors.[126] In 2005, Schmuñis and Cruz noted that, technically, universal screening for *T. cruzi* infection may not be cost-effective when donor infection prevalence is very low; quite aptly, they then observed that "it is far more difficult to explain this concept to the recipient of a *T. cruzi*-infected blood unit".[120]

Transmission of *T. cruzi* can also occur through transplantation of organs or bone marrow from infected donors, and may lead to severe disease in immuno-suppressed patients.[29,97,127,128] Transmission can occur when infected donors are not screened; when screening yields false-negative results; or when transplantation from a known infected donor proceeds because the benefits for the recipient are deemed to outweigh the risks—the management of which heavily relies on timely diagnosis and treatment.[29,81,128] Although the evidence is weak overall, the probability of transmission seems to be higher in heart (>75%) than in liver (~20%) or kidney (~10–15%) transplantation.[29,127,129] Immuno-suppressive therapy can also lead to (potentially severe) reactivation of Chagas disease in *T. cruzi*-infected individuals receiving organ transplantations, especially in heart recipients.[97,127,128,130] Again, pre-transplantation serological screening and risk management play critical roles in improving patient outcomes.[29,81,97,127,128] As with blood transfusion, international migration has outspread the risk of transplantation-mediated *T. cruzi* transmission to non-endemic settings.[12,129,131]

The genetic diversity of *Trypanosoma cruzi*

Trypanosoma cruzi is a genetically highly diverse parasite.[3,132] Extensive genotyping and phylogenetic studies have so far led to the recognition of seven discrete typing units (DTUs): TcI to TcVI plus Tcbat.[3] Understanding DTU distribution patterns, both in space and among vectors and vertebrate hosts including humans, is paramount for elucidating the epidemiological landscape of Chagas disease. Despite early indications and some suggestive patterns, there is no definite evidence for any clear–cut association between *T. cruzi* DTUs and distinct transmission cycles (e.g., 'sylvatic' *vs* 'domestic' or arboreal *vs* terrestrial), different transmission routes (e.g., vector-borne *vs* foodborne *vs* vertical), or the severity of human Chagas disease.[8,133,134] To our knowledge, no broad-scale representative survey looking at such putative associations has so far been conducted, and the evidence is therefore patchy; furthermore, the methods used for genotyping in the overwhelming majority of studies (from allozyme electrophoresis to PCR-based techniques) may not capture the true within-host diversity and dynamics of parasite strains.[135,136]

Current knowledge suggests that all DTUs from TcI to TcVI have a broad geographical distribution across the Americas.[3,132–137] While certain DTUs may be more frequently found in some regions, no DTU can be considered strictly endemic to a particular area, and

their overlapping distributions (Fig. 3) should be kept in mind when evaluating the possibility of mixed infections.[137] Overall, TcI emerges as the DTU most often detected in samples drawn from infected humans, but TcII, TcV, and TcVI also contribute to an important proportion of infections.[133] Notably, almost all DTUs are implicated in congenital transmission.[111] From a clinical perspective, the relations between DTUs and disease outcomes show high variability, and efforts are underway to establish whether there are robust associations (Table 2).[133,134,138]

TcI is itself also genetically highly diverse and has been linked to human Chagas disease in the USA, Mexico, Central America, and the Andean and Amazon regions; TcI infections can cause severe cardiomyopathy and meningoencephalitis, particularly in immunocompromised individuals, but have rarely been associated with digestive outcomes.[111,134] TcI has been found infecting mammals in the orders Didelphimorphia, Cingulata, Pilosa, Rodentia, Chiroptera, Carnivora, Artiodactyla, and Primates.[132,142] TcBat was first found in bats and later detected in a few humans and triatomine bugs; it seems to be phylogenetically closer to TcI than to other DTUs, and has so far been reported from Panama, Colombia, Ecuador, Chile, and Brazil.[134]

TcII and putative TcII/TcIII hybrid lineages (TcV and TcVI) are overall less genetically diverse than TcI and have been linked to chronic infections with cardiac and digestive disease in southern and central South America.[111] TcV is common in the Gran Chaco (which covers parts of Argentina, Paraguay, and Bolivia), where it may cause digestive and (relatively mild) heart disease.[143,144] Besides humans, there are records of TcV and/or TcVI in domestic (dogs, cats, guinea pigs, goats, sheep, pigs), wild (opossums, armadillos, rodents, bats), and captive mammals (macaques), as well as in *Triatoma*, *Panstrongylus*, *Rhodnius*, and *Mepraia* vectors.[132,135,141,142] Both TcV and TcVI have wide geographic distributions, with records spanning from the southern USA to Argentina.[132,135,142]

TcIII has been found circulating in sylvatic transmission cycles mainly among armadillos, but also infects rodents, marsupials, carnivores, bats, and non-human primates.[132,142,145–148] Species of *Panstrongylus*, *Triatoma*, and *Rhodnius* maintain TcIII transmission in both terrestrial and arboreal habitats.[8,132,142] TcIII infections have been reported in both foodborne-acute and chronic-indeterminate human Chagas disease patients, as well as in domestic dogs.[141,147,149] Patients coinfected with TcIII plus TcV or TcVI may develop chronic Chagas heart disease.[148,150] Overall, available TcIII records cover the whole of continental Latin America, from Mexico to Argentina and from semi-arid to rainforest environments.[132,142]

Trypanosoma cruzi TcIV infects humans, non-human primates, carnivores (including domestic dogs), bats, armadillos, and rodents, and can be transmitted by
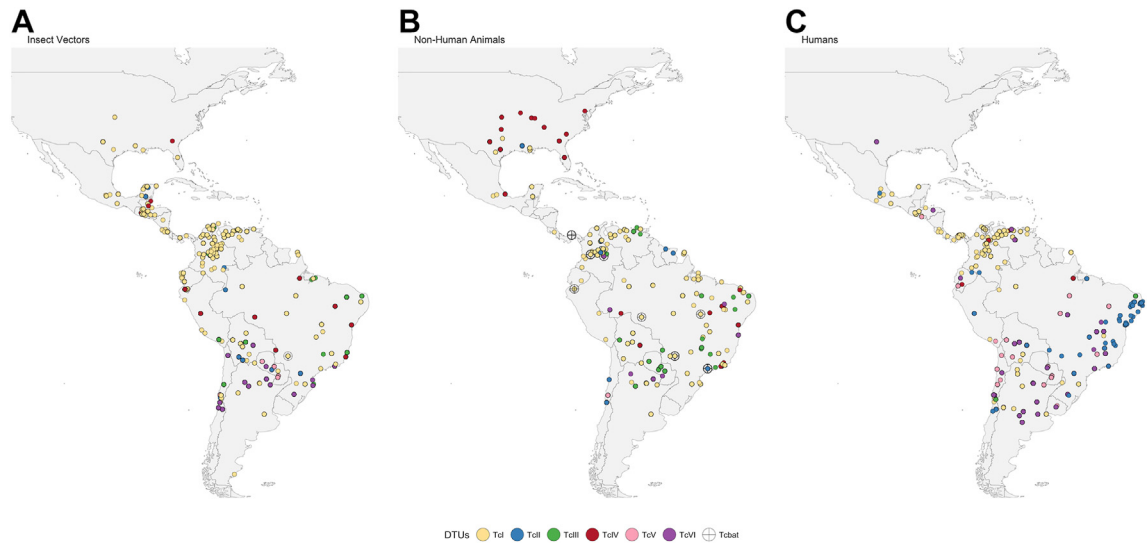
Fig. 3: **Distribution of DTUs in the Americas in vectors, non-human animals, and humans.** Distribution of DTUs identified in vectors (Panel A), non-human animals (Panel B), and humans (Panel C). The size or shape of the symbols does not indicate the exact geographic location or frequency as some points may be overlapped. Map created with R Software. Data source.[137]

species of *Triatoma*, *Panstrongylus*, *Rhodnius*, and *Dipetalogaster*.[132,135,142,151] TcIV has been implicated in acute vector-borne infections and human foodborne outbreaks, and can also cause chronic infections and heart disease.[113,146,152–156]

The striking levels of genetic diversity in *T. cruzi* have implications for our understanding of critical aspects of Chagas disease including clinical outcomes, parasite tissue tropism and pathogenesis, diagnosis (especially through serology), and epidemiology.[3,133,138,157,158] The complex interactions between parasite genetics, host genetic background and immune responses, and environmental factors likely contribute to the diverse clinical

outcomes observed across different regions.[3,138,159] Continued interdisciplinary research will be required to unravel the intricacies of *T. cruzi* DTU transmission dynamics and their implications for public health.

The epidemiology and burden of Chagas disease

Over the last two decades, the complexities of accurately estimating the burden of Chagas disease across the Americas have become increasingly apparent and understood. These complexities include substantial geographical variability, evolving epidemiological patterns, the extended period between initial infection (which is itself asymptomatic in about 95% of the cases) and chronic-symptom onset (which occurs in only 30–40% of those infected), gross underreporting of both cases and deaths and, in general, the scarcity of comprehensive data across both endemic and non-endemic regions.[160] The main challenges to estimating Chagas disease burden are summarised in Box 1.

Burden on individuals
Acute phase
Chagas disease incubation (i.e., the time interval between exposure to *T. cruzi* and the onset of symptoms—in the few symptomatic patients) generally lasts between one and two weeks for most transmission routes, but may extend to several weeks or months when transmission is mediated by solid-organ transplantation or blood transfusion.[13] The hallmark of acute Chagas disease is patent parasitaemia; the acute phase is asymptomatic or associated with mild, non-specific signs and symptoms in the

DTU	Chronic clinical manifestations		Transmission	
	Heart disease	Digestive disease	Vertical	Foodborne
TcI	X	X	?	X
TcII	X	X	X	?
TcIII	X	?	?	X
TcIV	X	X	?	X
TcV	X	X	X	?
TcVI	X	X	X	X
TcBat	?	?	?	?

'X' marks indicate known outcomes and routes; question marks ('?') emphasise that the absence of evidence does not necessarily mean that no association exists between specific DTUs and different clinical outcomes or transmission routes. Note that all DTUs can cause acute Chagas disease and can potentially be transmitted by triatomine bug vectors or infected blood/organs. Modified from.[141]

Table 2: *Trypanosoma cruzi* discrete typing units (DTUs): chronic clinical outcomes and transmission routes.

Box 1.
Challenges and opportunities for estimating Chagas disease burden

Challenges
Asymptomatic acute phase: Most new infections (about 95% of those mediated by vectors) do not produce any signs or symptoms; when they do, clinical manifestations are mostly non-specific (local skin inflammation ['chagoma'] at the site of parasite entry, fever, oedema, rash, malaise, asthenia, etc.), with only Romaña's sign (unilateral conjunctivitis with palpebral oedema) clearly helpful for clinical diagnosis. This leads to massive underdetection and underreporting of new cases and hampers the estimation of disease incidence.

Asymptomatic chronic infection: The indeterminate form of chronic Chagas disease lasts decades, with 60–70% of patients never evolving towards symptomatic forms. This means that most patients likely remain undiagnosed until they either donate blood or develop chronic disease. Delayed symptom onset hampers the estimation of both incidence and prevalence.

Surveillance systems and diagnosis access: Diagnostic approaches vary widely, with some countries relying on specific services like blood banks and others offering broader diagnosis access. The limited availability of diagnostic tests undermines the reliability of traditional surveillance methods for estimating disease burden and hampers the comparability of data across different regions.

Serosurvey limitations: While seroprevalence surveys are valuable, their focus on specific populations (often those deemed at higher risk) and/or age groups, as well as their variable methodological and testing approaches, limit generalisability and may introduce biases. Crucially, age-structured serological surveys can aid in estimating the historical force-of-infection (the rate at which susceptible individuals become infected) and contribute to parameterising infection-dynamics models.

Incidence calculations: True incidence is essentially impossible to measure and is hugely underreported. We can, however, use mathematical modelling and seroprevalence data to derive incidence, for instance using force-of-infection models.[42,43] Even simple methods can provide insights into the magnitude of underreporting. In Brazil, for example, contrasting data from the second National Serological Survey[44] with compulsory-notification records[45] suggests that only about 8.5% of new vector-mediated infections were reported to the Ministry of Health in 2001–2008.

Integration with demographic data: Accurately modelling Chagas disease burden requires integrating knowledge on infection dynamics with historical demographic and migration profiles at sub-national levels. The lack of detailed historical demographics for some countries in the Americas makes it difficult to achieve this integration.

Variability in transmission and progression parameters: Geographic, demographic, social, environmental, or (parasite, vector, and host) genetic factors may all affect the relative importance of different transmission routes and may all modulate disease progression and severity, further challenging the accurate estimation of Chagas disease burden; adaptable models that reflect local realities are needed to confront this challenge.

Opportunities for integrated modelling
Mathematical models of Chagas disease were first developed in the 1960s.[46] Currently, over 100 mathematical models[47] simulate different pieces of the epidemiological landscape including, e.g., parasite genetics,[48] vector life cycles,[49,50] routes and dynamics of transmission,[49,51] human dispersal,[49,52] and control interventions.[53] Despite these efforts, mathematical models have found very limited practical application. The primary concern is the absence of a comprehensive model integrating all relevant components related to Chagas disease transmission (including, e.g., domestic/peridomestic vector ecotopes, domestic and synanthropic mammal populations, and human demographics and behaviour) in changing ecological settings. The development of such a model would provide key guidance to decision-makers in specific situations, particularly if it is applied within an "adaptive management" framework.[54]

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vast majority of cases (see Box 1), and typically lasts between four and eight weeks.[13] Vector-borne, full-term congenital, and transfusion-related acute infections are often silent and rarely severe.[161] In contrast, foodborne infections often present with distinct and severe signs and symptoms including fever, malaise, oedema, anorexia, gastrointestinal illness, lymphadenopathy, hepatosplenomegaly, and acute myocarditis.[97,101] Case-fatality is high in foodborne acute Chagas disease, with recent reviews reporting crude rates of ~4% (2470 cases and 97 deaths; only peer-reviewed studies),[107] ~6.5% (568 cases and 37 deaths; peer-reviewed and unpublished studies),[98] or 8–35% (expert opinion).[161] The few peer-reviewed studies with $N > 100$ cases report ~1–7% case fatality, with upper CI limits ranging from ~5% to ~12%.[107] A meta-analysis of published and unpublished data

reported a substantially lower case-fatality rate estimate (~1%, 95% CI ~0–4%).[98]

Inoculum size (i.e., the number of parasites entering the host at the point of infection), which is usually larger in foodborne than in vector-borne cases,[20] is likely a key driver of disease severity and progression, with higher parasite loads linked to increased myocardial damage.[162,163] Patient age, *T. cruzi* strain/DTU,[164] and the promptness of medical treatment may also modulate the severity of acute *T. cruzi* infections. Pharmacological immunosuppression can lead to severe acute infections in transmission mediated by organ transplantation.[29,97,127,128]

Chronic phase
After the acute phase, most patients remain infected but asymptomatic; this 'indeterminate form' of chronic

Chagas disease usually lasts for decades, and only about 30–40% of patients develop symptomatic chronic disease (Box 1). Cardiac and digestive manifestations are distinct clinical outcomes of chronic Chagas disease.[55,97] While heart disease is widely reported across the Americas, digestive disease is much more common in southern South America (including Argentina, Bolivia, Chile, Paraguay, Uruguay, and parts of Brazil) than in northern South America, Central America, or Mexico. These geographical patterns are currently mainly attributed to variations in the predominant genotypes of *T. cruzi*.[2] Both heart and digestive forms of chronic symptomatic Chagas disease can be highly debilitating; heart failure and enlargement cause chest pain, dyspnoea, oedema, and thromboembolism (including brain and pulmonary embolisms); arrhythmias cause palpitations, dizziness, syncope, and sudden death (mainly from ventricular fibrillation); enlargement/dysfunction of the oesophagus leads to megaoesophagus and causes chronic regurgitation and dysphagia (which can lead to malnutrition), whereas enlargement/dysfunction of the colon leads to megacolon and causes severe constipation.[2,29,119]

About one-third of individuals infected with *T. cruzi* are expected to develop chronic heart disease, with an annual rate of progression of ~2–7%.[162] A recent systematic review and meta-analysis examining original studies of patients with confirmed Chagas disease (mainly from Brazil) found that the prevalence of chronic heart disease varies from 42.3% to 53.8%, while the prevalence of the digestive form varies between 18.4% and 25.4% in the Southern Cone of South America.[165] These variations may be driven by *T. cruzi* strain diversity, patient age and genetic background, or the level of endemicity (hence exposure to the parasite) within a given region, underscoring the complexity of clinical progression.[165]

The risk of death is 1.74 times higher (95% CI 1.5–2.0) in patients with chronic heart Chagas disease than in patients with comparable clinical profiles but without *T. cruzi* infection.[29,166] Sudden death is not a rare event and can be the first manifestation of the disease in patients with no previous signs or symptoms.[128,167] Mortality from chronic Chagas heart disease reaches 8.0% per year, mostly due to cardiovascular events (6.3%) including heart failure, arrhythmias, and thromboembolism; annual mortality is thus higher than in HIV/AIDS (7.0%), and similar to that seen in leukaemia (7.9%).[168,169] The degree of cardiomyopathy highly correlates with mortality, and there is some evidence suggesting that TcII may be associated with severe heart disease.[156] Between 2000 and 2019, Chagas disease was reported as the underlying cause of death in nearly 95,000 death certificates in Brazil; of those deaths, about 80% (77,000) were due to chronic heart disease and about 12–13% (12,000) to digestive chronic forms.[170]

Reactivation

Reactivation of Chagas disease is a severe, life-threatening acute condition that may occur in individuals infected with *T. cruzi* who later become immunocompromised, either as a result of immunosuppressive therapy (in, e.g., organ transplantation or cancer chemotherapy) or due to coinfection with HIV. It is estimated that around 13–20% of patients co-infected with HIV and *T. cruzi* may undergo Chagas disease reactivation, with the frequency depending mainly on HIV loads and CD4+ cell counts.[171–173] Meningoencephalitis and myocarditis are often seen in reactivation,[174] and male sex and low CD4+ counts may be associated with increased mortality.[173]

Burden on society: estimates of prevalence and incidence

Despite many challenges (see Box 1), there have been some efforts to model and estimate the burden of Chagas disease. In the early 2010s, when about 7.7–8.3 million people were likely infected with *T. cruzi* worldwide, the global costs of Chagas disease were estimated at US$ 7.2 billion per year and US$ 189 billion per lifetime, and the burden of disease was quantified at ~810,000 disability-adjusted life years (DALYs) lost annually.[175] At about the same time, the WHO/PAHO published model-based estimates suggesting that approximately 5.7 million people were infected, with nearly 1.2 million suffering from Chagas heart disease, in 21 Latin American (i.e., excluding the USA) countries or territories where Chagas disease is endemic.[28] The Global Burden of Disease (GBD)[30] Study has produced model-based estimates of prevalence since 1990; by 2010, global prevalence was estimated at 6.26 (5.46–7.13) million infected individuals, with a slight increase to 6.30 (5.42–7.21) million by 2021.[176] The GBD estimates a modest 11% decrease in global prevalence from 1990 to 2019.[30,177] Prevalence remains high in many rural areas of Latin America where recurrent invasion and infestation of (usually substandard) dwellings by *T. cruzi*-infected triatomines maintain endemic transmission.[178] Annual incidence estimates vary much more widely, from ~40,000 (WHO/PAHO)[28] to >150,000 (GBD)[176] new infections per year. This large discrepancy likely stems from differences in how demographic data were integrated into incidence models; for example, if country-specific populations are split into higher-risk (rural) and lower-risk (urban) strata, GBD-based estimates decrease to about 24,000 to 50,000 new cases per year, broadly matching the WHO/PAHO estimate. In Table 3 we present country-level estimates of Chagas disease prevalence and incidence within the Americas, and below we briefly comment on disease burden across subregions with enzootic/endemic *T. cruzi* transmission cycles.

Country	Source					
	WHO/PAHO 2010[28]		GBD 2010[a]		GBD 2021[a]	
	Prevalence (%)	Incidence (rate per 100 k)[b]	Prevalence (%)	Incidence (rate per 100 k)	Prevalence (%)	Incidence (rate per 100 k)
Canada	NR	NR	4474 (0.01)	NR	4413 (0.01)	NR
United States[c]	NR	NR	216,649 (0.07)	NR	241,691 (0.08)	NR
Mexico	876,458 (0.78)	6135/1788 (5/89)	912,265 (0.83)	28,198 (24.55)	1,182,286 (0.96)	32,469 (25.12)
Belize	1040 (0.33)	10/25 (3/333)	35 (0.01)	2 (0.51)	52 (0.01)	2 (0.55)
Guatemala	166,667 (1.23)	1275/164 (9/35)	92,591 (0.71)	3554 (26.10)	101,726 (0.67)	3460 (21.94)
Honduras	73,333 (0.92)	933/257 (11/126)	65,328 (0.85)	2523 (31.59)	78,686 (0.81)	2805 (27.74)
El Salvador	90,222 (1.30)	972/234 (13/187)	37,344 (0.64)	1215 (19.96)	37,367 (0.61)	1127 (17.47)
Nicaragua	29,300 (0.52)	383/138 (6/124)	37,382 (0.67)	1341 (23.39)	41,101 (0.64)	1362 (19.88)
Costa Rica	7667 (0.17)	10/61 (0.2/80)	20,587 (0.49)	618 (14.09)	21,486 (0.47)	571 (12.03)
Panama	18,337 (0.52)	175/40 (4/56)	20,219 (0.60)	601 (17.18)	21,111 (0.51)	605 (14.09)
Colombia[d]	437,960 (0.96)	5274/1046 (11/114)	121,954 (0.29)	3875 (8.71)	129,569 (0.27)	3772 (7.69)
Ecuador	199,872 (1.38)	2042/696 (14/317)	137,537 (0.95)	4106 (27.32)	144,098 (0.83)	3995 (22.12)
Venezuela	193,339 (0.71)	873/665 (3/110)	479,699 (1.78)	15,857 (57.05)	461,326 (1.79)	12,398 (46.56)
French Guiana, Guyana, and Suriname	12,600 (0.84)	280/18 (18/75)	NR	NR	NR	NR
Guyana	NR	NR	33 (<0.01)	2 (0.24)	31 (<0.01)	2 (0.22)
Suriname	NR	NR	40 (0.01)	2 (0.35)	42 (0.01)	2 (0.34)
Brazil	1,156,821 (0.61)	46[e]/571 (0.08/20)	1,857,485 (0.96)	58,955 (29.81)	2,058,211 (0.96)	60,162 (27.30)
Peru	127,282 (0.44)	2055/232 (7/38)	188,055 (0.66)	5686 (19.67)	196,295 (0.55)	5594 (15.42)
Bolivia	607,186 (6.10)	8087/616 (81/235)	559,626 (5.77)	17,142 (170.42)	469,788 (4.12)	13,589 (115.19)
Paraguay	184,669 (2.13)	297/525 (3/340)	31,794 (0.53)	1064 (17.30)	32,427 (0.47)	1019 (14.22)
Uruguay	7852 (0.24)	0[f]/20 (0/40)	25,016 (0.78)	0[f]	18,748 (0.57)	0[f]
Argentina	1,505,235 (3.64)	1078/1457 (2/210)	1,103,871 (2.80)	25,422 (61.84)	768,416 (1.76)	17,417 (38.29)
Chile[g]	119,660 (0.70)	0[f]/115 (0/46)	288,220 (1.81)	0[f]	236,228 (1.31)	0[f]

NR, not reported. [a]GBD estimates originally include measures of uncertainty not presented here; see[30] for details. [b]Overall/congenital (new cases per 100,000 population/new congenital cases per 100,000 live births). [c]Prevalence estimated at 288,000 in 2014–2018.[139] [d]Prevalence estimated at 506,000 in 2020.[42] [e]This is likely a gross underestimate and should be interpreted with caution; official notification records for 2010 include 130 new, confirmed cases of acute Chagas disease—1 vertical, 30 vector-borne, 63 foodborne, and 36 in which the transmission route was either unknown or not reported (https://datasus.saude.gov.br/informacoes-de-saude-tabnet/; accessed June 11 2024). If underreporting was similar for vertical (1/571, or ~0.175%) and non-vertical transmission, then 26,266 non-vertical transmission-mediated cases would have had to occur to yield the '46 new cases' estimate. [f]Assumed zero (i.e., not modelled) based on PAHO certificates of interruption of transmission. [g]In Chile, incidence was nonzero in each year between 2007 and 2021, with, respectively, 44, 115, 268, 438, 520, 24, 1, 2, 2, 1, 2, 4, 14, 18, and 7 new, confirmed cases of acute Chagas disease reported by the Ministry of Health (1460 new cases overall); based on these official data, the incidence rate was ~2.6 per 100,000 population in 2010, but just ~0.04 per 100,000 in 2021.[140] We did not find any official data from Uruguay.

Table 3: Model-based estimates of Chagas disease prevalence and incidence in the Americas.

Chagas disease burden in the United States of America

The USA has well-documented enzootic transmission of *T. cruzi*, involving 11 triatomine species and various mammalian hosts.[12] Nearly 30 human cases due to local, vector-borne transmission were documented between 1950 and 2015[179]; Arizona, Arkansas, California, Louisiana, Mississippi, Missouri, Tennessee, and Texas have all reported autochthonous cases.[180] The majority of *T. cruzi* infections in the USA, however, correspond to Latin American immigrants who became infected in their home countries.[12] Recent estimates from age-structured models indicate that ~288,000 infected adults were living in the USA in 2014–2018, with ~10,000 locally acquired cases.[139] GBD estimates for 2021 suggest that nearly 242,000 people (95% uncertainty interval, 202,000–284,000) may be infected in the country (Table 3).[30]

Chagas disease burden in Mexico

Mexico faces a considerable Chagas disease burden, with estimates suggesting that ~900,000–1.2 million people are infected (Table 3).[28,176] Official reports, however, acknowledge only a few thousand cases annually.[181] Historically, *T. cruzi* infection was predominantly noted in Mexico's southern states, but recent research highlights the presence of the disease also in the northern regions—with both migration and local transmission likely contributing to this trend.[182,183] Annual incidence estimates vary between ~8000 and > 30,000 (Table 3).[28,176] The most recent incidence estimates (for 2021) range from 41.9 (Chiapas) to 19.3 (Campeche) new cases per 100,000 population.[30]

Chagas disease burden in Central America

Approximately 12% of the population of Central America (Belize, Guatemala, El Salvador, Honduras, Nicaragua, Costa Rica, and Panama) lives at risk of Chagas disease.[28] Identified in El Salvador as early as 1913, the disease remains underreported across the region.[28,184] Current estimates suggest that between 300,000 and 400,000 individuals are infected in Central

America, with annual incidence varying from ~5000 to ~10,000 (Table 3).[28,176]

Chagas disease burden in South America
South America faces the highest global burden of Chagas disease, with ~4–5 million infected people—mainly in Brazil, Argentina, Bolivia, and Venezuela (Table 3).[28,176] *Trypanosoma cruzi* strains, triatomine vectors, mammalian hosts, and the clinical manifestations of the disease are all particularly diverse in South America.[185] Incidence estimates vary between ~26,000 and ~120,000 new cases per year, with rates as high as ~80–115 per 100,000 population in Bolivia (Table 3).[28,176]

Chagas disease burden among Latin American migrants
By 2020, it was estimated that ~32 million Latin American and Caribbean (LAC) migrants were living in countries or territories where Chagas disease is not endemic—about 26 million in the USA and 5 million in Europe.[186] Although population-representative data are lacking, studies using convenience sampling have reported prevalence values ranging from 0.2% to 20%.[187] Understanding the prevalence in the country of origin is crucial. For example, in the USA the frequency of *T. cruzi* infection is substantially higher among immigrants from El Salvador than among those from Mexico.[139] In Europe, seroprevalence among LAC migrants was estimated at 4.2% on average (up to 18.1% among Bolivians) in 2012.[188] Other surveys have found infection frequencies from 0.3% among LAC blood donors (France, 2007–2008)[189] to 12.8% for LAC migrants in general (Switzerland, 2008),[190] with intermediate values in LAC migrants living in, e.g., London (1.27% in 2011)[191] or Spain (2.1% in 2018),[192] and among pregnant LAC women living in Switzerland (2.0% to 9.7% in 2007–2008).[193,194]

Chagas disease prevention and management
Primary prevention: vector control-surveillance, donor screening, and the multinational initiatives
Efforts to eliminate non-native 'primary' vectors, and in particular *Triatoma infestans* and *Rhodnius prolixus*, have relied heavily on residual-insecticide spraying, with some programmes also including housing improvement—mainly by replacing mud walls, earthen floors, and thatched roofs—and community-oriented initiatives.[25,75,195] In spite of major advances, continuous surveillance remains crucial to control transmission mediated by native vectors—of which 140+ species occur in the Americas.[25,70,73,196] In 1991, the health ministers of Argentina, Brazil, Bolivia, Chile, Paraguay, and Uruguay launched the Initiative of the Southern Cone Countries for the control of Chagas disease (INCOSUR), which aimed primarily at eliminating domestic *T. infestans* populations and interrupting transfusion-related *T. cruzi* transmission.[197] Similar initiatives were

later established throughout the region, including Central America and Mexico, the Andean countries, and Amazonia.[25] The progress of these subregional initiatives is regularly reviewed by PAHO.[198,199] Up to the present, PAHO has issued certifications of interruption of *T. cruzi* transmission by non-native populations of two vector species: *T. infestans* in Uruguay, Chile, Brazil, Paraguay, and parts of Argentina, Bolivia, and Peru; and *R. prolixus* in Mexico, Guatemala, Belize, Honduras, El Salvador, Nicaragua, Costa Rica, and parts of Colombia.[73,200]

In the complex epidemiological landscape of Chagas disease, involving native and non-native vector species and diverse transmission routes, PAHO has recently revised its certification approach to also consider the 'elimination of Chagas disease as a public health problem'.[201] The process of certification in this case entails (i) demonstrating successful control efforts against all vector species and transmission routes (leading to "zero incidence" of vector-borne and transfusion-mediated infections), and (ii) having a structured and functional programme for Chagas disease surveillance, diagnosis, and treatment with guaranteed adequate coverage levels (with, e.g., screening of all pregnant women and all blood or organ donors; diagnosis offered to all childbearing-aged women at risk and to all babies born to seropositive mothers; and 'timely and suitable' treatment of all cases detected—whether congenital, acute, or chronic). Certifications of interruption of transmission and elimination of the disease as a public health problem are subject to review every five years.[201] Below we provide a brief overview of the regional initiatives, with a focus on vector-borne transmission (see[25] for further details).

The Initiative of Central America and Mexico (IPCAM) includes Mexico, Belize, Guatemala, El Salvador, Honduras, Nicaragua, Costa Rica, and Panama, and primarily targets non-native *R. prolixus* and native *T. dimidiata sensu lato* (*s.l.*).[25] Notably, *R. prolixus* was found infesting houses and peridomestic structures in rural Oaxaca, Mexico after the region was certified as free from transmission by this non-native vector in 2009.[202] More recently, a focus of infestation by *T. infestans* (which is native to the Chaco and central Andes in South America) has been reported in coastal Colima, Mexico.[203] *Triatoma dimidiata s.l.* is native to the region and often reinvades and reinfests dwellings—as do, to different degrees, several other species including *T. ryckmani*, *T. nitida*, *T. barberi*, *T. pallidipennis*, *T. longipennis*, *T. huehuetenanguensis*, or *R. pallescens*. The long-term control of vector-borne Chagas disease in the subregion will probably require integrating insecticide spraying with household-level environmental management and community involvement.[25]

The Initiative of the Andean Countries (IPA) includes Colombia, Venezuela, Ecuador and Peru. Non-native *R. prolixus* occur in north-western Colombia, non-native *T. dimidiata* in coastal Ecuador, and non-

native *T. infestans* in parts of south-western Peru. These introduced populations can, in principle, be eliminated through large-scale control campaigns.[25] However, *R. prolixus* is native to the Orinoco savannahs and adjacent dry ecoregions,[204,205] and *T. dimidiata sensu stricto* (*s.s.*) to most of western Colombia and likely parts of northern Venezuela[7,206,207]; persistent reinvasion and reinfestation of dwellings by these and several other native vectors (e.g., *T. maculata* in Colombia and Venezuela or *R. ecuadoriensis* and *Panstrongylus chinai* in Ecuador and Peru) is common, and long-term control-surveillance will be required to effectively curb transmission.[25]

The Amazon Countries (AMCHA) Initiative includes parts of Colombia, Ecuador, Peru, Bolivia, Brazil, and Venezuela plus Guyana, Suriname, and French Guiana. Although stable house infestation by triatomines is not common in the region, there is an extensive list of sylvatic vectors that often invade human dwellings in both rural and urban areas.[25] Transmission mediated by these vectors can be either direct, leading to an overall prevalence of human infection of about 1–2% (but up to 4–5% in some subregions), or through contamination of food or beverages, with clustered outbreaks of orally-transmitted disease.[25,68,208] House-infestation foci, however, are common in northernmost Brazil (*T. maculata*), in the middle-upper Marañón Valley in Peru (*P. lignarius/ herreri*), and in parts of Bolivia (*R. stali*).[25,73,208]

The Initiative of the Southern Cone Countries (INCOSUR) includes Brazil, Peru, Bolivia, Chile, Argentina, Paraguay, and Uruguay. Non-native *T. infestans* populations were once widespread in rural settings across the region; extensive control campaigns eliminated them from Uruguay, most of Brazil, and parts of Paraguay, Argentina, Peru, Bolivia, and Chile, leading to substantial reductions in the incidence and prevalence of human *T. cruzi* infections.[25,75] In spite of major advances, prevalence remains high in parts of Bolivia and, to a lesser extent, Paraguay, Brazil, or Argentina, and native vectors maintain transmission throughout the Southern Cone.[25] Some *T. infestans* populations have adapted to urban/ periurban environments in, e.g., Arequipa, Peru[209]; San Juan, Argentina[210]; and Cochabamba, Bolivia.[211] The control of urban infestations and transmission is particularly challenging and will require innovative tactics.[212,213] Crucially, *T. infestans* is native to the dry Chaco and the Bolivian montane dry forests,[7] and other locally native species (*T. brasiliensis*, *P. megistus*, *T. sordida*, *T. pseudomaculata* and many more) often infest houses and peridomestic structures. Control of these domestic/ peridomestic native vectors is challenging, with reinfestations leading to persistent transmission.[25,214]

Secondary/tertiary prevention: diagnosis, treatment, and integral patient care

As we have emphasised throughout this review, millions of people across the Americas (and thousands in Europe, Asia, and Oceania) carry chronic *T. cruzi* infections, and tens of thousands probably become infected each year—mainly *via* direct or indirect contact with vectors but also vertically or, in a minority of cases, through blood transfusion, organ transplantation, or laboratory accidents. Timely diagnosis and adequate, integral care are critical to the fundamental rights to life, health, and well-being[215] of people infected with *T. cruzi*, whatever their age, gender, origins, background, or means—and no matter whether the infection is acute or chronic; symptomatic or silent; vector-borne, foodborne, congenital, blood-borne, or acquired through transplantation; or caused by one particular *T. cruzi* DTU or another. Below we present a quick overview of Chagas disease diagnosis and treatment; for more comprehensive reviews of these and related topics, see the other series papers on clinical progression and severity,[55] diagnosis,[57] and vaccines and therapeutics.[58]

The diagnosis of Chagas disease is challenging. First, the likelihood of clinical suspicion is low, both because most infections (acute and chronic) are asymptomatic or cause nonspecific signs/symptoms and because many caregivers lack awareness about Chagas disease.[216] When there is clinical suspicion and laboratory diagnosis is sought, several biological and technical shortcomings weaken the performance of available procedures. In acute and congenital infections, diagnosis usually aims at detecting parasites or their DNA (the 'targets for detection') in blood samples; even if parasitaemia is common in the acute phase, there is no guarantee that all samples drawn from infected patients will contain those targets—and, when they do, neither parasitological nor molecular tests have perfect (i.e., exactly 100%) sensitivity.[217,218] The problem of imperfect target availability only worsens in chronic infections, where parasitaemia is sparser and likely intermittent.[217,219] Serological testing has the advantage of targeting a widely bio-available class of molecules—antibodies—that are present in essentially any serum sample drawn from an infected patient.[217,219] Serology has, however, several major drawbacks; first, most serological tests lack validation across different populations and may have low specificity, so that at least two positive serological tests based on different antigenic principles are required for diagnosis[29]; in addition, sensitivity and specificity can also vary with *T. cruzi* genotype/DTU and/or antigenic makeup.[220] Rapid diagnostic (immunochromatographic) tests, while promising and especially well suited for point-of-care testing and large-scale screening/surveys in resource-limited settings, have variable sensitivity and may perform very poorly in some subregions.[221,222] Although new biomarkers with high specificity and wide bio-availability would likely enhance diagnosis and perhaps inform prognosis,[217,219] the most critical issue is still the lack of equitable access to available testing methods and algorithms—and, when needed, to integral patient care.[25,223]

Treatment of Chagas disease involves not only the use of specific anti-*T. cruzi* drugs, but also the treatment and management of chronic heart and digestive disease and their complications.[97] Two drugs, benznidazole and nifurtimox, are indicated in all acute infections, congenital infections, chronically infected children, and disease reactivation. Treatment of women of child-bearing age with chronic asymptomatic infections seems to reduce the risk of vertical transmission and is therefore recommended, whereas the benefits are less clear for other adults with indeterminate chronic disease. Currently, PAHO recommends that benznidazole and nifurtimox should not be used in clinical practice for treating adult patients with moderate or severe symptomatic chronic forms; this recommendation, however, is 'conditional' and based on evidence of 'moderate' strength.[97,224] We note that, in general, designing clinical trials for trypanocidal drug efficacy is complex, as critical endpoints (chronic heart or digestive disease, death) may take decades to come about; clinical findings, moreover, can be confounded by many factors including parasite genetics, human population peculiarities, access to healthcare, reinfection, or re-treatment.[225] Consequently, the strength of the evidence supporting the recommendations about anti-*T. cruzi* treatment we have just outlined is at best moderate.[224] Although benznidazole is overall well tolerated, an estimated 17–35% of chronically infected adult patients interrupt their treatment due to side effects.[224] Recent evidence suggests that shorter regimens, which may enhance adherence and increase treatment coverage, are non-inferior to standard regimens in terms of parasitological response as measured by qPCR.[226] While new trypanocidal drugs are sorely needed, there has been virtually no progress over the last half-century; an exception is a benzoxaborole prodrug (AN15368) that has yielded promising results in non-human primate chronic-infection models.[227,228] One critical issue is that the effective treatment of chronic Chagas disease requires drugs that kill extra- and intracellular parasites including 'dormant' forms that are protected from, and hence resistant to, the trypanocidal action of standard doses of benznidazole or nifurtimox.[229] Preclinical research suggests that AN15368 and modified benznidazole regimens might be useful against both bloodstream and intracellular (active and dormant) *T. cruzi* forms.[227,230]

Importantly, timely anti-*T. cruzi* treatment can prevent the evolution of asymptomatic or mild infections towards the chronic symptomatic forms of Chagas disease, which can be highly debilitating and impose a heavy burden on patients and society.[97,128] Patients with chronic symptomatic forms of Chagas heart disease may need additional specialised care for heart failure (from diet to diuretic, antihypertensive, or beta-blocker drugs to heart transplantation), arrhythmias (from amiodarone or beta blockers to catheter ablation, implantable cardioverter-defibrillators, or pacemakers), and thromboembolism (acetylsalicylic acid, warfarin).[97] The management of chronic digestive forms spans from diet and counselling to surgery. Megaoesophagus treatment aims at relieving dysphagia by facilitating the passage of food through the lower oesophageal sphincter; this may involve diet/counselling and/or the use of drugs that relax smooth-muscle fibres, physical (pneumatic-balloon) dilatation, or surgery. Treating megacolon may also involve diet (with a focus on increasing water intake), counselling (on, e.g., avoiding food or drugs that may induce constipation), the use of laxatives or enemas, manual removal of faecalomas, or surgery—including emergency surgery in cases of volvulus, haemorrhage, obstruction, or perforation.[97]

Search strategy and selection criteria

We searched PubMed for articles published in English using a search algorithm with "Chagas disease", "*Trypanosoma cruzi*", "Epidemiology", and "Americas". The final references were selected based on relevance to the scope of this Review.

Conclusions and outlook: a future free of Chagas disease?

Chagas disease remains a major public health challenge in the Americas. Over six million people are infected, and most of them face substantial barriers to accessing essential healthcare, including diagnosis and treatment. Despite considerable progress in controlling transmission through universal blood-bank and organ-donor screening and the elimination of many non-native, domiciliated vector populations, active transmission—still mainly mediated by vectors—persists. While current intervention strategies have led to major advances, they are unlikely to deliver complete success. Widespread native vector populations continue to invade, infest, and reinfest human dwellings, bridging sylvatic, peridomestic, and domestic *T. cruzi* transmission cycles (Fig. 1). A highly diverse array of vectors and non-human hosts maintain sylvatic transmission of *T. cruzi* from the USA to southern South America (Figs. 1–3); eradication of Chagas disease is, therefore, biologically implausible: even if non-native vector populations are effectively eliminated, dozens of native vector species will continue transmitting *T. cruzi* across tropical-subtropical America. All estimates suggest that tens of thousands of new vector-borne human infections occur each year in the Americas, yet, crucially, most of them remain invisible to surveillance systems—and the alarms remain, therefore, silent. Vertical and foodborne transmission have become increasingly prominent in the current epidemiological landscape, but this should

not obscure the fact that the majority of new cases is most likely vector-borne. Congenital Chagas disease presents unique challenges; specific diagnostic and treatment protocols for pregnant women (and, ideally, childbearing-aged women with a history of potential exposure) and newborns are needed to prevent transmission. The complex nature of Chagas disease transmission, in sum, demands a holistic healthcare strategy covering from vector surveillance to integral patient care, and highlights the critical need for in-depth ecological, epidemiological, clinical, and public-health research.[25,128] Such research should aim to i) understand the complex interplay between sylvatic and domestic/peridomestic transmission cycles, including the roles played by native vectors across the Americas; ii) assess the impact of *T. cruzi* DTUs on transmission patterns, disease severity, and treatment outcomes; iii) develop enhanced diagnostic and therapeutic approaches; iv) generate more accurate disease burden estimates (e.g., using age-structured dynamic models); and v) use implementation science to develop and test integrative control-surveillance strategies within the diverse ecological, socio-economic and climatic contexts where transmission still occurs. Bridging these knowledge gaps is vital for crafting more effective long-term interventions, for consolidating the substantial achievements of control programmes and initiatives, and perhaps for developing adaptive strategies in which living close to *T. cruzi* vectors and hosts does not necessarily translate into full-blown Chagas disease.

References

1 Aufderheide AC, Salo W, Madden M, et al. A 9000-year record of Chagas disease. *Proc Natl Acad Sci U S A*. 2004;101:2034–2039.

2 Bern C. Chagas' disease. *N Engl J Med*. 2015;373:456–466.

3 Zingales B, Miles MA, Campbell DA, et al. The revised *Trypanosoma cruzi* subspecific nomenclature: rationale, epidemiological relevance and research applications. *Infect Genet Evol*. 2012;12:240–253.

4 Ventura-Garcia L, Roura M, Pell C, et al. Socio-cultural aspects of Chagas disease: a systematic review of qualitative research. *PLoS Negl Trop Dis*. 2013;7:e2410.

5 Liu Q, Chen J, Zhou X-N. Preparedness for Chagas disease spreading worldwide. *Infect Dis Poverty*. 2020;9:44.

6 Lent H, Wygodzinsky P. Revision of the Triatominae (Hemiptera, Reduviidae), and their significance as vectors of Chagas' disease. *Bull Am Mus Nat History*. 1979;163:125–520.

7 Monteiro FA, Weirauch C, Felix M, Lazoski C, Abad-Franch F. Evolution, systematics, and biogeography of the Triatominae, vectors of Chagas disease. *Adv Parasitol*. 2018;99:265–344.

8 Abad-Franch F, Gurgel-Gonçalves R. The ecology and natural history of wild Triatominae in the Americas. In: Guarneri AA, Lorenzo MG, eds. *Triatominae - The biology of Chagas disease vectors. Entomology in Focus*. Cham: Springer; 2021:387–445; 5.

9 Rodríguez-Monguí E, Cantillo-Barraza O, Prieto-Alvarado FE, Cucunubá ZM. Heterogeneity of *Trypanosoma cruzi* infection rates in vectors and animal reservoirs in Colombia: a systematic review and meta-analysis. *Parasit Vectors*. 2019;12:308.

10 Noireau F, Diosque P, Jansen AM. *Trypanosoma cruzi:* adaptation to its vectors and its hosts. *Vet Res*. 2009;40:26.

11 Jansen AM, Xavier SCDC, Roque ALR. *Trypanosoma cruzi* transmission in the wild and its most important reservoir hosts in Brazil. *Parasit Vectors*. 2018;11:502.

12 Bern C, Messenger LA, Whitman JD, Maguire JH. Chagas disease in the United States: a public health approach. *Clin Microbiol Rev*. 2019;33. https://doi.org/10.1128/CMR.00023-19.

13 Rassi A Jr, Rassi A, Marin-Neto JA. Chagas disease. *Lancet*. 2010;375:1388–1402.

14 Klein MD, Proaño A, Noazin S, Sciaudone M, Gilman RH, Bowman NM. Risk factors for vertical transmission of Chagas disease: a systematic review and meta-analysis. *Int J Infect Dis*. 2021;105:357–373.

15 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.

16 Santana KH, Oliveira LGR, Barros de Castro D, Pereira M. Epidemiology of Chagas disease in pregnant women and congenital transmission of *Trypanosoma cruzi* in the Americas: systematic review and meta-analysis. *Trop Med Int Health*. 2020;25:752–763.

17 Lynn MK, Rodriguez Aquino MS, Cornejo Rivas PM, et al. Chagas disease maternal seroprevalence and maternal-fetal health outcomes in a parturition cohort in Western El Salvador. *Trop Med Infect Dis*. 2023;8. https://doi.org/10.3390/tropicalmed8040233.

18 Coura JR. The main sceneries of Chagas disease transmission. The vectors, blood and oral transmissions- a comprehensive review. *Mem Inst Oswaldo Cruz*. 2015;110:277–282.

19 Roellig DM, Ellis AE, Yabsley MJ. Oral transmission of *Trypanosoma cruzi* with opposing evidence for the theory of carnivory. *J Parasitol*. 2009;95:360–364.

20 Robertson LJ, Havelaar AH, Keddy KH, Devleesschauwer B, Sripa B, Torgerson PR. The importance of estimating the burden of disease from foodborne transmission of *Trypanosoma cruzi*. *PLoS Negl Trop Dis*. 2024;18:e0011898.

21 Shikanai-Yasuda MA, Carvalho NB. Oral transmission of Chagas disease. *Clin Infect Dis*. 2012;54:845–852.

22 Schmunis GA. Epidemiology of Chagas disease in non-endemic countries: the role of international migration. *Mem Inst Oswaldo Cruz*. 2007;102(Suppl 1):75–85.

23 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;52:1913–1921.

24 Huprikar S, Bosserman E, Patel G, et al. Donor-derived *Trypanosoma cruzi* infection in solid organ recipients in the United States, 2001-2011. *Am J Transplant*. 2013;13:2418–2425.

25 Rojasde Arias A, Monroy C, Guhl F, Sosa-Estani S, Santos WS, Abad-Franch F. Chagas disease control-surveillance in the Americas: the multinational initiatives and the practical impossibility of interrupting vector-borne *Trypanosoma cruzi* transmission. *Mem Inst Oswaldo Cruz*. 2022;117:e210130.

26 Nouvellet P, Dumonteil E, Gourbière S. The improbable transmission of *Trypanosoma cruzi* to human: the missing link in the

dynamics and control of Chagas disease. *PLoS Negl Trop Dis.* 2013;7:e2505.

27 Pan American Health Organization. Chagas disease. https://www.paho.org/en/topics/chagas-disease. Accessed May 28, 2024.

28 World Health Organization. Chagas disease in Latin America: an epidemiological update based on 2010 estimates. *Wkly Epidemiol Rec.* 2015;6:33–43.

29 World Health Organization. In: *Control of chagas disease.* Second report of the WHO Expert Committee. World Health Organ Tech Rep Ser; 2002;905:i–vi, 1–109.

30 Institute for Health Metrics and Evaluation (IHME). GBD results. https://vizhub.healthdata.org/gbd-results/; 2024. Accessed May 28, 2024.

31 Salvatella R, Irabedra P, Castellanos LG. Interruption of vector transmission by native vectors and 'the art of the possible'. *Mem Inst Oswaldo Cruz.* 2014;109:122–125.

32 Dias JCP, Silveira AC, Schofield CJ. The impact of Chagas disease control in Latin America: a review. *Mem Inst Oswaldo Cruz.* 2002;97:603–612.

33 Rural population - Latin America & Caribbean. World bank open data. https://data.worldbank.org/indicator/SP.RUR.TOTL?locations=ZJ. Accessed May 28, 2024.

34 Naciones Unidas. Portal de desigualdades en América Latina. CEPALSTAT. https://statistics.cepal.org/portal/inequalities/housing-and-basic-services.html?lang=es&indicator=260. Accessed May 28, 2024.

35 Pan American Health Organization. *70% of people with Chagas don't know they're infected.* Pan American Health Organization; 2021. https://www.paho.org/en/news/13-4-2021-70-people-chagas-dont-know-theyre-infected. Accessed May 28, 2024.

36 Sgambatti de Andrade ALS, Zicker F, de Oliveira RM, et al. Randomised trial of efficacy of benznidazole in treatment of early *Trypanosoma cruzi* infection. *Lancet.* 1996;348:1407–1413.

37 Cançado JR. Long term evaluation of etiological treatment of Chagas disease with benznidazole. *Rev Inst Med Trop Sao Paulo.* 2002;44:29–37.

38 Chaves GC, Abi-Saab Arrieche M, Rode J, et al. Estimación de la demanda de medicamentos antichagásicos: una contribución para el acceso en América Latina. *Rev Panam Salud Publica.* 2017;41:e45.

39 Manne-Goehler J, Reich MR, Wirtz VJ. Access to care for Chagas disease in the United States: a health systems analysis. *Am J Trop Med Hyg.* 2015;93:108–113.

40 Cucunubá ZM, Manne-Goehler JM, Díaz D, et al. How universal is coverage and access to diagnosis and treatment for Chagas disease in Colombia? A health systems analysis. *Soc Sci Med.* 2017;175:187–198.

41 Briceño-León R. La enfermedad de Chagas en las Américas: una perspectiva de ecosalud. *Cad Saúde Pública.* 2009;25:S71–S82.

42 Ledien J, Cucunubá ZM, Parra-Henao G, et al. From serological surveys to disease burden: a modelling pipeline for Chagas disease. *Philos Trans R Soc Lond B Biol Sci.* 2023;378:20220278.

43 Cucunubá ZM, Nouvellet P, Conteh L, et al. Modelling historical changes in the force-of-infection of Chagas disease to inform control and elimination programmes: application in Colombia. *BMJ Glob Health.* 2017;2:e000345.

44 Ostermayer AL, Passos ADC, Silveira AC, Ferreira AW, Macedo V, Prata AR. O inquérito nacional de soroprevalência de avaliação do controle da doença de Chagas no Brasil (2001-2008). *Rev Soc Bras Med Trop.* 2011;44(Suppl 2):108–121.

45 DATASUS – Ministério da Saúde. https://datasus.saude.gov.br/. Accessed April 4, 2024.

46 Silva GR da. Sôbre o modêlo catalítico reversível aplicado ao estudo da cinética epidemiológica da infecção chagásica. *Rev Saude Publica.* 1969;3:23–29.

47 Nouvellet P, Cucunubá ZM, Gourbière S. Ecology, evolution and control of Chagas disease: a century of neglected modelling and a promising future. *Adv Parasitol.* 2015;87:135–191.

48 Devillers H, Raymond Lobry J, Menu F. An agent-based model for predicting the prevalence of *Trypanosoma cruzi* I and II in their host and vector populations. *J Theor Biol.* 2008;255:307–315.

49 Pelosse P, Kribs-Zaleta CM, Ginoux M, Rabinovich JE, Gourbière S, Menu F. Influence of vectors' risk-spreading strategies and environmental stochasticity on the epidemiology and evolution of vector-borne diseases: the example of Chagas' disease. *PLoS One.* 2013;8:e70830.

50 Stevens L, Rizzo DM, Lucero DE, Pizarro JC. Household model of Chagas disease vectors (Hemiptera: Reduviidae) considering

domestic, peridomestic, and sylvatic vector populations. *J Med Entomol.* 2013;50:907–915.

51 Ramalho E, Albuquerque J, Cristino C, et al. Congenital and blood transfusion transmission of Chagas disease: a framework using mathematical modeling. *Complexity.* 2018;2018:1589016.

52 Lozada-Yavina R, Marchant C, Cancino-Faure B, Hernández-Rodríguez EW, Córdova-Lepe F. A description of the epidemiological dynamics of Chagas disease via mathematical modeling. *Acta Trop.* 2023;243:106930.

53 Spagnuolo AM, Shillor M, Stryker GA. A model for Chagas disease with controlled spraying. *J Biol Dynam.* 2011;5:299–317.

54 Shea K, Possingham HP, Murdoch WW, Roush R. Active adaptative management in insect pest and weed control: intervention with a plan for learning. *Ecol Appl.* 2002;12:927–936.

55 Nunes MCP, Bern C, Clark EH, Teixeira AL, Molina I. Clinical aspects of Chagas disease progression and severity. Lancet Reg Health Am.

56 Forsyth CJ, Ni AH, Hamer S, et al. Climate change and trypanosoma cruzi transmission in north America, Central America, and the Caribbean. Lancet Microbe, *In press.*

57 Schijman AG, Alonso-Padilla J, Britto C, Cp HB. Retrospect, Advances and challenges in Chagas disease diagnosis: a comprehensive review. *Lancet Reg Health Am.* 2024;36:100821.

58 Pinazo MJ, Malchiodi EL, Ioset JR, Bivona AE, Gollob KJ Dutra W. O Challenges and advancements in human Chagas disease vaccine and therapy development: from Bench to Field. Lancet Microbe. *In press.*

59 Rengifo-Correa L, Rodríguez-Moreno Á, Becker I, et al. Risk of a vector-borne endemic zoonosis for wildlife: hosts, large-scale geography, and diversity of vector-host interactions for *Trypanosoma cruzi.* *Acta Trop.* 2024;251:107117.

60 Gottdenker NL, Calzada JE, Saldaña A, Carroll CR. Association of anthropogenic land use change and increased abundance of the Chagas disease vector *Rhodnius pallescens* in a rural landscape of Panama. *Am J Trop Med Hyg.* 2011;84:70–77.

61 Santos WS, Gurgel-Gonçalves R, Garcez LM, Abad-Franch F. Deforestation effects on *Attalea* palms and their resident *Rhodnius,* vectors of Chagas disease, in eastern Amazonia. *PLoS One.* 2021;16:e0252071.

62 Varian CP, Saldaña A, Calzada JE, et al. Food web structure and microenvironment affect Chagas disease vector infection and abundance in a rural landscape. *Ecosphere.* 2023;14. https://doi.org/10.1002/ecs2.4347.

63 Cohen JE, Gürtler RE. Modeling household transmission of American trypanosomiasis. *Science.* 2001;293:694–698.

64 Valença-Barbosa C, Lima MM, Sarquis O, Bezerra CM, Abad-Franch F. Modeling disease vector occurrence when detection is imperfect II: drivers of site-occupancy by synanthropic *Triatoma brasiliensis* in the Brazilian northeast. *PLoS Negl Trop Dis.* 2014;8:e2861.

65 Schaub GA. Interaction of, triatomines and the microbiota of the vectors-A review. *Microorganisms.* 2024;12. https://doi.org/10.3390/microorganisms12050855.

66 Gürtler RE Fernandez MP, Cardinal MV. Eco-epidemiology of the domestic vector-borne transmission of *Trypanosoma cruzi.* In: Guarneri AA, ed. *Triatominae: the biology of Chagas disease vectors.* Springer International Publishing; 2021:447–489.

67 Salcedo-Porras N Lowenberger C. The immune system of triatomines. In: Guarneri AA, ed. *Triatominae - The biology of Chagas disease vectors, Entomology in Focus, vol 5.* Cham: Springer; 2021:307–344.

68 Abad-Franch F, Diotaiuti L, Gurgel-Gonçalves R, Gürtler RE. Certifying the interruption of Chagas disease transmission by native vectors: cui bono? *Mem Inst Oswaldo Cruz.* 2013;108:251–254.

69 Abad-Franch F. A simple, biologically sound, and potentially useful working classification of Chagas disease vectors. *Mem Inst Oswaldo Cruz.* 2016;111:649–651.

70 Waleckx E, Gourbière S, Dumonteil E. Intrusive versus domiciliated triatomines and the challenge of adapting vector control practices against Chagas disease. *Mem Inst Oswaldo Cruz.* 2015;110:324–338.

71 Ceccarelli S, Balsalobre A, Cano ME, et al. *Datos de ocurrencia de triatominos americanos del Laboratorio de Triatominos del CEPAVE (CONICET-UNLP). Version 1.6.* Occurrence Dataset; 2022. https://doi.org/10.15468/fbywtn.

72 Ceccarelli S, Balsalobre A, Cano ME, et al. *Datos de ocurrencia de triatominos presentes en Argentina del Laboratorio de Triatominos del*

CEPAVE *(CONICET-UNLP). Version 1.2.* Occurrence Dataset; 2020. https://doi.org/10.15468/ak8aax.

73 Abad-Franch F, Diotaiuti L, Gurgel-Gonçalves R, Gürtler RE. On bugs and bias: improving Chagas disease control assessment. *Mem Inst Oswaldo Cruz.* 2014;109:125–130.

74 Hashimoto K, Schofield CJ. Elimination of *Rhodnius prolixus* in central America. *Parasit Vectors.* 2012;5:45.

75 Schofield CJ, Jannin J, Salvatella R. The future of Chagas disease control. *Trends Parasitol.* 2006;22:583–588.

76 Oliveira I, Torrico F, Muñoz J, Gascon J. Congenital transmission of Chagas disease: a clinical approach. *Expert Rev Anti Infect Ther.* 2014;8:945–956.

77 Abras A, Ballart C, Fernández-Arévalo A, et al. Worldwide control and management of Chagas disease in a new era of globalization: a close look at congenital *Trypanosoma cruzi* infection. *Clin Microbiol Rev.* 2022;35:e0015221.

78 Messenger LA, Bern C. Congenital Chagas disease: current diagnostics, limitations and future perspectives. *Curr Opin Infect Dis.* 2018;31:415–421.

79 Picado A, Cruz I, Redard-Jacot M, et al. The burden of congenital Chagas disease and implementation of molecular diagnostic tools in Latin America. *BMJ Glob Health.* 2018;3:e001069.

80 Pan American Health Organization. *EMTCT Plus. Framework for elimination of mother-to-child transmission of HIV, Syphilis, Hepatitis B, and Chagas.* Whasington, DC: PAHO; 2017. https://iris.paho.org/handle/10665.2/34306. Accessed May 28, 2024.

81 Shikanai Yasuda MA. Emerging and reemerging forms of *Trypanosoma cruzi* transmission. *Mem Inst Oswaldo Cruz.* 2022;117: e210033.

82 Buekens P, Cafferata ML, Alger J, et al. Congenital transmission of *Trypanosoma cruzi* in Argentina, Honduras, and Mexico: an observational prospective study. *Am J Trop Med Hyg.* 2018;98:478–485.

83 Carlier Y, Sosa-Estani S, Luquetti AO, Buekens P. Congenital Chagas disease: an update. *Mem Inst Oswaldo Cruz.* 2015;110:363–368.

84 Carlier Y, Truyens C. Congenital Chagas disease as an ecological model of interactions between *Trypanosoma cruzi* parasites, pregnant women, placenta and fetuses. *Acta Trop.* 2015;151:103–115.

85 Amorín B, Pérez L. Chagas congénito de segunda generación en Uruguay: Primer caso sintomático descrito en el país. *Arch Pediatr Urug.* 2016;87:245–252.

86 Sánchez Negrette O, Mora MC, Basombrío MA. High prevalence of congenital *Trypanosoma cruzi* infection and family clustering in Salta, Argentina. *Pediatrics.* 2005;115:e668–e672.

87 Danesi E, Fabbro DL, Segura EL, Sosa-Estani S. Higher congenital transmission rate of *Trypanosoma cruzi* associated with family history of congenital transmission. *Rev Soc Bras Med Trop.* 2020;53: e20190560.

88 Fabbro DL, Danesi E, Olivera V, et al. Trypanocide treatment of women infected with *Trypanosoma cruzi* and its effect on preventing congenital Chagas. *PLoS Negl Trop Dis.* 2014;8. https://doi.org/10.1371/journal.pntd.0003312.

89 Murcia L, Simón M, Carrilero B, Roig M, Segovia M. Treatment of infected women of childbearing age prevents congenital *Trypanosoma cruzi* infection by eliminating the parasitemia detected by PCR. *J Infect Dis.* 2017;215:1452–1458.

90 Sosa-Estani S, Cura E, Velazquez E, Yampotis C, Segura EL. Etiological treatment of young women infected with *Trypanosoma cruzi,* and prevention of congenital transmission. *Rev Soc Bras Med Trop.* 2009;42:484–487.

91 Moscatelli G, Moroni S, García-Bournissen F, et al. Prevention of congenital Chagas through treatment of girls and women of childbearing age. *Mem Inst Oswaldo Cruz.* 2015;110:507–509.

92 Álvarez MG, Vigliano C, Lococo B, Bertocchi G, Viotti R. Prevention of congenital Chagas disease by Benznidazole treatment in reproductive-age women. An observational study. *Acta Trop.* 2017;174:149–152.

93 Carlier Y, Altcheh J, Angheben A, et al. Congenital Chagas disease: updated recommendations for prevention, diagnosis, treatment, and follow-up of newborns and siblings, girls, women of childbearing age, and pregnant women. *PLoS Negl Trop Dis.* 2019;13: e0007694.

94 Organización Panamericana de la Salud. *Nuevas generaciones sin la infección por el VIH, la sífilis, la hepatitis B y la enfermedad de Chagas en las Américas 2018. ETMI Plus.* Washington DC: OPS; 2019. https://iris.paho.org/bitstream/handle/10665.2/50993/9789275320679_spa.pdf?sequence=1&isAllowed=y.

95 Cucunubá ZM, Valencia-Hernández CA, Puerta CJ, et al. First Colombian consensus on congenital Chagas and clinical approach for women of child-bearing age diagnosed with Chagas. *Infection.* 2017;21:255–266.

96 Eickhoff CS, Dunn BA, Sullivan NL, Hoft DF. Comparison of the infectivity of *Trypanosoma cruzi* insect-derived metacyclic trypomastigotes after mucosal and cutaneous contaminative challenges. *Mem Inst Oswaldo Cruz.* 2013;108:508–511.

97 Dias JCP, Ramos AN Jr, Gontijo ED, et al. 2nd Brazilian Consensus on Chagas disease, 2015. *Rev Soc Bras Med Trop.* 2016;40 (Suppl 1):3–60.

98 López-García A, Gilabert JA. Oral transmission of Chagas disease from a One Health approach: a systematic review. *Trop Med Int Health.* 2023;28:689–698.

99 Dias JCP. Notas sobre o *Trypanosoma cruzi* e suas catacterísticas bio-ecológicas, como agente de enfermidades transmitidas por alimentos. *Rev Soc Bras Med Trop.* 2006;39:370–375.

100 Deane MP, Lenzi HL, Jansen A. *Trypanosoma cruzi*: invertebrate cycles in the same mammal host, the oppsoum *Didelphis marsupialis. Mem Inst Oswaldo cruz.* 1984;79:513–515.

101 Beatty NL, Arango-Ferreira C, Gual-Gonzalez L, Zuluaga S, Nolan MS, Cantillo-Barraza O. Oral Chagas disease in Colombia-confirmed and suspected routes of transmission. *Trop Med Infect Dis.* 2024;9. https://doi.org/10.3390/tropicalmed9010014.

102 Ramírez JD, Montilla M, Cucunubá ZM, Floréz AC, Zambrano P, Guhl F. Molecular epidemiology of human oral Chagas disease outbreaks in Colombia. *PLoS Negl Trop Dis.* 2013;7:e2041.

103 Andrade DV, Gollob KJ, Dutra WO. Acute Chagas disease: new global challenges for an old neglected disease. *PLoS Negl Trop Dis.* 2014;8:e3010.

104 Norman FF, López-Vélez R. Chagas disease and breast-feeding. *Emerg Infect Dis.* 2013;19:1561–1566.

105 da Silva NN, Clausell DT, Nólibos H, et al. Surto epidêmico da doença de Chagas com provável contaminação oral. *Rev Inst Med Trop Sao Paulo.* 1968;10:265–276.

106 Noya BA, Díaz-Bello Z, Colmenares C, et al. Update on oral Chagas disease outbreaks in Venezuela: epidemiological, clinical and diagnostic approaches. *Mem Inst Oswaldo Cruz.* 2015;110:377–386.

107 Bruneto EG, Fernandes-Silva MM, Toledo-Cornell C, et al. Case-fatality from orally-transmitted acute Chagas disease: a systematic review and meta-analysis. *Clin Infect Dis.* 2021;72:1084–1092.

108 Blanchet D, Brenière SF, Schijman AG, et al. First report of a family outbreak of Chagas disease in French Guiana and post-treatment follow-up. *Infect Genet Evol.* 2014;28:245–250.

109 Freitas VLT, Piotto MR, Esper HR, et al. Detection of *Trypanosoma cruzi* DTUs TcI and TcIV in two outbreaks of orally-transmitted Chagas disease in the Northern region of Brazil. *Rev Inst Med Trop Sao Paulo.* 2023;65:e7.

110 Barbosa MD, Ferreira JM, Arcanjo AR, et al. Chagas disease in the State of Amazonas: history, epidemiological evolution, risks of endemicity and future perspectives. *Rev Soc Bras Med Trop.* 2015;48(Suppl 1):27–33.

111 Messenger LA, Miles MA, Bern C. Between a bug and a hard place: *Trypanosoma cruzi* genetic diversity and the clinical outcomes of Chagas disease. *Expert Rev Anti Infect Ther.* 2015;13:995–1029.

112 Olivera MJ, Rincón Acevedo CY, Olivera AJ, Mendez-Cardona S, Vera Soto MJ. Addressing Chagas disease from a One Health perspective: risk factors, lessons learned and prevention of oral transmission outbreaks in Colombia. *Sci One Health.* 2024;3: 100066.

113 Valente SA, da Costa Valente V, das Neves Pinto AY, et al. Analysis of an acute Chagas disease outbreak in the Brazilian Amazon: human cases, triatomines, reservoir mammals and parasites. *Trans R Soc Trop Med Hyg.* 2009;103:291–297.

114 Xavier SC das C, Roque ALR, Bilac D, et al. *Distantiae* transmission of *Trypanosoma cruzi*: a new epidemiological feature of acute Chagas disease in Brazil. *PLoS Negl Trop Dis.* 2014;8:e2878.

115 Cantillo-Barraza O, Bedoya SC, Xavier SCC, et al. *Trypanosoma cruzi* infection in domestic and synanthropic mammals such as potential risk of sylvatic transmission in a rural area from north of Antioquia, Colombia. *Parasite Epidemiol Control.* 2020;11: e00171.

116 de Sousa DRT, de Oliveira Guerra JA, Ortiz JV, et al. Acute Chagas disease associated with ingestion of contaminated food in Brazilian western Amazon. *Trop Med Int Health.* 2023;28:541–550.

117 Dias JCP, Brener S. Chagas' disease and blood transfusion. *Mem Inst Oswaldo Cruz.* 1984;79:139–147.

118 Schmuñis GA. *Trypanosoma cruzi*, the etiologic agent of Chagas' disease: status in the blood supply in endemic and nonendemic countries. *Transfusion*. 1991;31:547–557.

119 World Health Organization. Control of Chagas disease. Report of a WHO expert committee. *World Health Organ Tech Rep Ser*. 1991;811:1–95.

120 Schmunis GA, Cruz JR. Safety of the blood supply in Latin America. *Clin Microbiol Rev*. 2005;18:12–29.

121 Pan American Health Organization. *Supply of blood for transfusion in Latin America and Caribbean countries 2016-2017*. Washington DC: PAHO; 2020. https://doi.org/10.37774/9789275121719.

122 Bwititi PT, Browne J. Seroprevalence of *Trypanosoma cruzi* in blood donors at the national blood transfusion services – Guyana. *West Indian Med J*. 2012;61:559–563.

123 Dodd RY, Groves JA, Townsend RL, et al. Impact of one-time testing for *Trypanosoma cruzi* antibodies among blood donors in the United States. *Transfusion*. 2019;59:1016–1023.

124 Bern C, Montgomery SP, Katz L, Caglioti S, Stramer SL. Chagas disease and the US blood supply. *Curr Opin Infect Dis*. 2008;21:476–482.

125 Garcia MN, Woc-Colburn L, Rossmann SN, et al. *Trypanosoma cruzi* screening in Texas blood donors, 2008-2012. *Epidemiol Infect*. 2016;144:1010–1013.

126 O'Brien SF, Scalia V, Goldman M, et al. Selective testing for *Trypanosoma cruzi*: the first year after implementation at Canadian blood services. *Transfusion*. 2013;53:1706–1713.

127 Pérez-Molina JA, Molina I. Chagas disease. *Lancet*. 2018;391:82–94.

128 de Sousa AS, Vermeij D, Ramos AN Jr, Luquetti AO. Chagas disease. *Lancet*. 2024;403:203–218.

129 Pierrotti LC, Carvalho NB, Amorin JP, Pascual J, Kotton CN, López-Vélez R. Chagas disease recommendations for solid-organ transplant recipients and donors. *Transplantation*. 2018;102:S1–S7.

130 Altclas JD, Barcan L, Nagel C, Lattes R, Riarte A. Organ transplantation and Chagas disease. *JAMA*. 2008;299:1134–1135.

131 Gonzalez-Sanz M, Crespillo-Andújar C, Chamorro-Tojeiro S, Monge-Maillo B, Perez-Molina JA, Norman FF. Chagas disease in Europe. *Trop Med Infect Dis*. 2023;8.

132 Brenière SF, Waleckx E, Barnabé C. Over six thousand *Trypanosoma cruzi* strains classified into discrete typing units (DTUs): attempt at an inventory. *PLoS Negl Trop Dis*. 2016;10:e0004792.

133 Zingales B, Bartholomeu DC. *Trypanosoma cruzi* genetic diversity: impact on transmission cycles and Chagas disease. *Mem Inst Oswaldo Cruz*. 2022;117:e210193.

134 Magalhães LMD, Gollob KJ, Zingales B, Dutra WO. Pathogen diversity, immunity, and the fate of infections: lessons learned from *Trypanosoma cruzi* human-host interactions. *Lancet Microbe*. 2022;3:e711–e722.

135 Dumonteil E, Desale H, Tu W, et al. Intra-host *Trypanosoma cruzi* strain dynamics shape disease progression: the missing link in Chagas disease pathogenesis. *Microbiol Spectr*. 2023;11:e0423622.

136 Herrera C, Majeau A, Didier P, Falkenstein KP, Dumonteil E. *Trypanosoma cruzi* diversity in naturally infected nonhuman primates in Louisiana assessed by deep sequencing of the mini-exon gene. *Trans R Soc Trop Med Hyg*. 2019;113:281–286.

137 Velásquez-Ortiz N, Herrera G, Hernández C, Muñoz M, Ramírez JD. Discrete typing units of Trypanosoma cruzi: geographical and biological distribution in the Americas. *Sci Data*. 2022;9:360.

138 Zingales B. *Trypanosoma cruzi* genetic diversity: something new for something known about Chagas disease manifestations, serodiagnosis and drug sensitivity. *Acta Trop*. 2018;184:38–52.

139 Irish A, Whitman JD, Clark EH, Marcus R, Bern C. Updated estimates and mapping for prevalence of Chagas disease among adults, United States. *Emerg Infect Dis*. 2022;28:1313–1320.

140 Departamento de Epidemiología del Ministerio de Salud de Chile. Bases ENO. Bases ENO. https://epi.minsal.cl/bases-de-datos-eno/. Accessed June 13, 2024.

141 Zingales B, Macedo AM. Fifteen years after the definition of *Trypanosoma cruzi* DTUs: what have we learned? *Life*. 2023;13.

142 Izeta-Alberdi A, Ibarra-Cerdeña CN, Moo-Llanes DA, Ramsey JM. Geographical, landscape and host associations of *Trypanosoma cruzi* DTUs and lineages. *Parasit Vectors*. 2016;9:631.

143 Monje-Rumi MM, Brandán CP, Ragone PG, et al. *Trypanosoma cruzi* diversity in the Gran Chaco: mixed infections and differential host distribution of TcV and TcVI. *Infect Genet Evol*. 2015;29:53–59.

144 Gürtler RE, Cardinal MV. Reservoir host competence and the role of domestic and commensal hosts in the transmission of *Trypanosoma cruzi*. *Acta Trop*. 2015;151:32–50.

145 Guhl F, Ramírez JD. Retrospective molecular integrated epidemiology of Chagas disease in Colombia. *Infect Genet Evol*. 2013;20:148–154.

146 Monteiro WM, Magalhães LK, Santana Filho FS, et al. *Trypanosoma cruzi* TcIII/Z3 genotype as agent of an outbreak of Chagas disease in the Brazilian Western Amazonia. *Trop Med Int Health*. 2010;15:1049–1051.

147 Martins K, Andrade Cde M, Barbosa-Silva AN, et al. *Trypanosoma cruzi* III causing the indeterminate form of Chagas disease in a semi-arid region of Brazil. *Int J Infect Dis*. 2015;39:68–75.

148 Rodrigues-Dos-Santos Í, Melo MF, de Castro L, et al. Exploring the parasite load and molecular diversity of *Trypanosoma cruzi* in patients with chronic Chagas disease from different regions of Brazil. *PLoS Negl Trop Dis*. 2018;12:e0006939.

149 Garzón EA, Barnabé C, Córdova X, et al. *Trypanosoma cruzi* isoenzyme variability in Ecuador: first observation of zymodeme III genotypes in chronic chagasic patients. *Trans R Soc Trop Med Hyg*. 2002;96:378–382.

150 Burgos JM, Diez M, Vigliano C, et al. Molecular identification of *Trypanosoma cruzi* discrete typing units in end-stage chronic Chagas heart disease and reactivation after heart transplantation. *Clin Infect Dis*. 2010;51:485–495.

151 Flores-López CA, Esquivias-Flores EA, Guevara-Carrizales A. Phylogenetic description of *Trypanosoma cruzi* isolates from *Dipetalogaster maxima*: occurrence of TcI, TcIV, and TcIV – USA. *Infect Genet Evol*. 2023;113:105465.

152 Ramírez JD, Guhl F, Rendón LM, Rosas F, Marin-Neto JA, Morillo CA. Chagas cardiomyopathy manifestations and *Trypanosoma cruzi* genotypes circulating in chronic chagasic patients. *PLoS Negl Trop Dis*. 2010;4:e899.

153 Guhl F, Auderheide A, Ramírez JD. From ancient to contemporary molecular eco-epidemiology of Chagas disease in the Americas. *Int J Parasitol*. 2014;44:605–612.

154 Carrasco HJ, Segovia M, Llewellyn MS, et al. Geographical distribution of *Trypanosoma cruzi* genotypes in Venezuela. *PLoS Negl Trop Dis*. 2012;6:e1707.

155 Perez-Molina JA, Poveda C, Martinez-Perez A, et al. Distribution of *Trypanosoma cruzi* discrete typing units in Bolivian migrants in Spain. *Infect Genet Evol*. 2014;21:440–442.

156 Tavares de Oliveira M, Fuzo CA, da Silva MC, et al. Correlation of TcII discrete typing units with severe chronic Chagas cardiomyopathy in patients from various Brazilian geographic regions. *PLoS Negl Trop Dis*. 2022;16:e0010713.

157 Ricci AD, Bracco L, Salas-Sarduy E, et al. The *Trypanosoma cruzi* antigen and epitope atlas: antibody specificities in Chagas disease patients across the Americas. *Nat Commun*. 2023;14:1850.

158 Majeau A, Dumonteil E, Herrera C. Identification of highly conserved Trypanosoma cruzi antigens for the development of a universal serological diagnostic assay. *Emerg Microbes Infect*. 2024;13:2315964.

159 Couto-Silva CM, Nunes K, Venturini G, et al. Indigenous people from Amazon show genetic signatures of pathogen-driven selection. *Sci Adv*. 2023;9:eabo0234.

160 Stanaway JD, Roth G. The burden of Chagas disease: estimates and challenges. *Glob Heart*. 2015;10:139–144.

161 Franco-Paredes C, Villamil-Gómez WE, Schultz J, et al. A deadly feast: elucidating the burden of orally acquired acute Chagas disease in Latin America - public health and travel medicine importance. *Travel Med Infect Dis*. 2020;36:101565.

162 Nunes MCP, Beaton A, Acquatella H, et al. Chagas cardiomyopathy: an update of current clinical knowledge and management: a scientific statement from the American Heart Association. *Circulation*. 2018;138:e169–e209.

163 de Oliveira MT, Schmidt A, da Silva MC, Donadi EA, da Silva JS, Marin-Neto JA. Parasitic load correlates with left ventricular dysfunction in patients with chronic Chagas cardiomyopathy. *Front Cardiovasc Med*. 2021;8:741347.

164 Coura JR. Chagas disease: what is known and what is needed-a background article. *Mem Inst Oswaldo Cruz*. 2007;102(Suppl 1):113–122.

165 Ramos Nascimento B, Dias Nassar Naback A, Marino Pena Santos B, et al. Prevalence of clinical forms of Chagas disease: a systematic review and meta-analysis - data from the RAISE study. *Lancet Reg Health Am*. 2024;30:100681.

166 Cucunubá ZM, Okuwoga O, Basáñez M-G, Nouvellet P. Increased mortality attributed to Chagas disease: a systematic review and meta-analysis. *Parasit Vectors*. 2016;9:42.

167 Keegan R, Yeung C, Baranchuk A. Sudden cardiac death risk stratification and prevention in Chagas disease: a non-systematic review of the literature. *Arrhythm Electrophysiol Rev*. 2020;9:175–181.

168 Chadalawada S, Rassi A Jr, Samara O, et al. Mortality risk in chronic Chagas cardiomyopathy: a systematic review and meta-analysis. *ESC Heart Fail*. 2021;8:5466–5481.

169 Maron BJ. Clinical course and management of hypertrophic cardiomyopathy. *N Engl J Med*. 2018;379:655–668.

170 Martins-Melo FR, Castro MC, Werneck GL. Levels and trends in Chagas disease-related mortality in Brazil, 2000-2019. *Acta Trop*. 2021;220:105948.

171 Sartori AMC, Ibrahim KY, Nunes Westphalen EV, et al. Manifestations of Chagas disease (American trypanosomiasis) in patients with HIV/AIDS. *Ann Trop Med Parasitol*. 2007;101:31–50.

172 Reimer-McAtee MJ, Mejia C, Clark T, et al. HIV and Chagas Disease: an evaluation of the use of real-time quantitative polymerase chain reaction to measure levels of *Trypanosoma cruzi* parasitemia in HIV patients in Cochabamba, Bolivia. *Am J Trop Med Hyg*. 2021;105:643–650.

173 Shikanai-Yasuda MA, Mediano MFF, Novaes CTG, et al. Clinical profile and mortality in patients with *T. cruzi*/HIV co-infection from the multicenter data base of the 'Network for healthcare and study of *Trypanosoma cruzi*/HIV co-infection and other immunosuppression conditions'. *PLoS Negl Trop Dis*. 2021;15:e0009809.

174 Bern C. Chagas disease in the immunosuppressed host. *Curr Opin Infect Dis*. 2012;25:450–457.

175 Lee BY, Bacon KM, Bottazzi ME, Hotez PJ. Global economic burden of Chagas disease: a computational simulation model. *Lancet Infect Dis*. 2013;13:342–348.

176 GBD 2019 Diseases and Injuries Collaborators. Global burden of 369 diseases and injuries in 204 countries and territories, 1990-2019: a systematic analysis for the global burden of disease study 2019. *Lancet*. 2020;396:1204–1222.

177 Gómez-Ochoa SA, Rojas LZ, Echeverría LE, Muka T, Franco OH. Global, regional, and national trends of Chagas disease from 1990 to 2019: comprehensive analysis of the Global Burden of Disease Study. *Glob Heart*. 2022;17:59.

178 Mejía-Jaramillo AM, Agudelo-Uribe LA, Dib JC, Ortiz S, Solari A, Triana-Chávez O. Genotyping of *Trypanosoma cruzi* in a hyperendemic area of Colombia reveals an overlap among domestic and sylvatic cycles of Chagas disease. *Parasit Vectors*. 2014;7:108.

179 Montgomery SP, Parise ME, Dotson EM, Bialek SR. What do we know about Chagas disease in the United States? *Am J Trop Med Hyg*. 2016;95:1225–1227.

180 Beatty NL, Klotz SA. Autochthonous Chagas disease in the United States: how are people getting infected? *Am J Trop Med Hyg*. 2020;103:967–969.

181 Ibáñez-Cervantes G, León-García G, Castro-Escarpulli G, et al. Evolution of incidence and geographical distribution of Chagas disease in Mexico during a decade (2007-2016). *Epidemiol Infect*. 2018;147:e41.

182 González-Guzmán S, González-Cano P, Bagu ET, et al. Seroprevalence of *Trypanosoma cruzi* in eight blood banks in Mexico. *Arch Med Res*. 2022;53:625–633.

183 Rivas N, González-Guzmán S, Alejandre-Aguilar R. First record of *Triatoma barberi* Usinger, 1939 (Hemiptera: Reduviidae) in northern State of Mexico, Mexico. *J Vector Ecol*. 2018;43:337–339.

184 Ponce C. Current situation of Chagas disease in Central America. *Mem Inst Oswaldo Cruz*. 2007;102(Suppl 1):41–44.

185 Flores-Ferrer A, Marcou O, Waleckx E, Dumonteil E, Gourbière S. Evolutionary ecology of Chagas disease; what do we know and what do we need? *Evol Appl*. 2018;11:470–487.

186 International Organization for Migration. Americas and the Caribbean. https://www.iom.int/americas-and-caribbean-0. Accessed March 2, 2024.

187 Conners EE, Vinetz JM, Weeks JR, Brouwer KC. A global systematic review of Chagas disease prevalence among migrants. *Acta Trop*. 2016;156:68–78.

188 Requena-Méndez A, Aldasoro E, de Lazzari E, et al. Prevalence of Chagas disease in Latin-American migrants living in Europe: a systematic review and meta-analysis. *PLoS Negl Trop Dis*. 2015;9:e0003540.

189 El Ghouzzi M-H, Boiret E, Wind F, et al. Testing blood donors for Chagas disease in the Paris area, France: first results after 18 months of screening. *Transfusion*. 2010;50:575–583.

190 Jackson Y, Gétaz L, Wolff H, et al. Prevalence, clinical staging and risk for blood-borne transmission of Chagas disease among Latin American migrants in Geneva, Switzerland. *PLoS Negl Trop Dis*. 2010;4:e592.

191 Requena-Méndez A, Moore DAJ, Subirà C, Muñoz J. Addressing the neglect: Chagas disease in London, UK. *Lancet Glob Health*. 2016;4:e231–e233.

192 Navarro M, Reguero L, Subirà C, Blázquez-Pérez A, Requena-Méndez A. Estimating chagas disease prevalence and number of underdiagnosed, and undertreated individuals in Spain. *Travel Med Infect Dis*. 2022;47:102284.

193 Jackson Y, Myers C, Diana A, et al. Congenital transmission of Chagas disease in Latin American immigrants in Switzerland. *Emerg Infect Dis*. 2009;15:601–603.

194 Martinez de Tejada B, Jackson Y, Paccolat C. Irion O. Dépistage et prise en charge de la maladie de Chagas congénitale à Genève. *Rev Med Suisse*. 2009;5(2091–2):2094–2096.

195 World Health Organization. *Integrating neglected tropical diseases into global health and development: fourth WHO report on neglected tropical diseases*. World Health Organization; 2018. https://www.who.int/publications/i/item/9789241565448.

196 Gürtler RE, Kitron U, Cecere MC, Segura EL, Cohen JE. Sustainable vector control and management of Chagas disease in the Gran Chaco, Argentina. *Proc Natl Acad Sci U S A*. 2007;104:16194–16199.

197 Pan American Health Organization. *Iniciativa del Cono Sur : Agosto 1991-Diciembre 1992: Estado actual de las acciones para la eliminación de la transmisión vectorial e interrupción de la transmisión transfusional del Tripanosoma Cruzi*. Washington DC: OPS; 1992. https://iris.paho.org/handle/10665.2/38214. Accessed March 9, 2024.

198 Organización Panamericana de la Salud. *Control, interrupción de la transmisión y eliminación de la enfermedad de Chagas como problema de salud pública. Guía de evaluación, verificación y validación*. Organización Panamericana de la Salud; 2019. https://doi.org/10.37774/9789275121528.

199 Organización Mundial de Ia. Salud – Organización Mundial de la Salud –División de Control de Enfermedades. Procesos de control de triatomíneos y control de la transmisión transfusional de *Trypanosoma cruzi*. *Rev Patol Trop*. 2002;31:269–282.

200 Organización Panamericana de la Salud. Enfermedad de Chagas – Transmisión por el principal vector. https://www.paho.org/en/documents/map-chagas-vectorial-transmission-2019-spanish-only; 2019. Accessed June 11, 2024.

201 Organización Panamericana de la Salud. *Guía metodológica para evaluaciones externas de la interrupción de la transmisión y la eliminación de la enfermedad de Chagas como problema de salud pública*. Whashington DC: OPS; 2023. https://doi.org/10.37774/9789275327494.

202 Antonio-Campos A, Nicolás-Cruz A, Girón-Arias JI, Rivas N, Alejandre-Aguilar R. Presence of *Rhodnius prolixus* Stål, 1859 (Hemiptera: Reduviidae) in Oaxaca, Mexico, ten years after the certification of its elimination. *J Vector Ecol*. 2019;44:293–295.

203 Martínez-Hernández F, Villalobos G, Montañez-Valdez OD, Martínez-Ibarra JA. A new record of the introduced species *Triatoma infestans* (Hemiptera: Reduviidae) in Mexico. *J Med Entomol*. 2022;59:2150–2157.

204 Fitzpatrick S, Feliciangeli MD, Sanchez-Martin MJ, Monteiro FA, Miles MA. Molecular genetics reveal that silvatic *Rhodnius prolixus* do colonise rural houses. *PLoS Negl Trop Dis*. 2008;2:e210.

205 Guhl F, Pinto N, Aguilera G. Sylvatic triatominae: a new challenge in vector control transmission. *Mem Inst Oswaldo Cruz*. 2009;104(Suppl 1):71–75.

206 Bargues MD, Klisiowicz DR, Gonzalez-Candelas F, et al. Phylogeography and genetic variation of *Triatoma dimidiata*, the main Chagas disease vector in Central America, and its position within the genus *Triatoma*. *PLoS Negl Trop Dis*. 2008;2:e233.

207 Monteiro FA, Peretolchina T, Lazoski C, et al. Phylogeographic pattern and extensive mitochondrial DNA divergence disclose a species complex within the Chagas disease vector *Triatoma dimidiata*. *PLoS One*. 2013;8:e70974.

208 Aguilar HM, Abad-Franch F, Dias JCP, Junqueira ACV, Coura JR. Chagas disease in the Amazon region. *Mem Inst Oswaldo Cruz*. 2007;102(Suppl 1):47–56.

209 Delgado S, Ernst KC, Pumahuanca MLH, et al. A country bug in the city: urban infestation by the Chagas disease vector *Triatoma infestans* in Arequipa, Peru. *Int J Health Geogr*. 2013;12:48.

210 Provecho YM, Fernández MDP, Salvá L, et al. Urban infestation by *Triatoma infestans* (Hemiptera: Reduviidae), an overlooked phenomena for Chagas disease in Argentina. *Mem Inst Oswaldo Cruz*. 2021;116:e210056.

211 Medrano-Mercado N, Ugarte-Fernandez R, Butrón V, et al. Urban transmission of Chagas disease in Cochabamba, Bolivia. *Mem Inst Oswaldo Cruz*. 2008;103:423–430.

212 Levy MZ, Malaga Chavez FS, Cornejo Del Carpio JG, Vilhena DA, McKenzie FE, Plotkin JB. Rational spatio-temporal strategies for controlling a Chagas disease vector in urban environments. *J R Soc Interface*. 2010;7:1061–1070.

213 Levy MZ, Barbu CM, Castillo-Neyra R, et al. Urbanization, land tenure security and vector-borne Chagas disease. *Proc Biol Sci*. 2014;281:20141003.

214 Espinoza N, Borrás R, Abad-Franch F. Chagas disease vector control in a hyperendemic setting: the first 11 years of intervention in Cochabamba, Bolivia. *PLoS Negl Trop Dis*. 2014;8:e2782.

215 Human rights. https://www.who.int/news-room/fact-sheets/detail/human-rights-and-health. Accessed June 12, 2024.

216 Marcus R, Henao-Martínez AF, Nolan M, et al. Recognition and screening for Chagas disease in the USA. *Ther Adv Infect Dis*. 2021;8:20499361211046086.

217 Abad-Franch F. Chagas disease diagnosis and cure assessment: getting formally hierarchical about a naturally hierarchical problem. *PLoS Negl Trop Dis*. 2020;14:e0008751.

218 Morillo CA, Marin-Neto JA, Avezum A, et al. Randomized trial of benznidazole for chronic Chagas' cardiomyopathy. *N Engl J Med*. 2015;373:1295–1306.

219 Abad-Franch F. Trypanosoma cruzi parasitemia in chronic Chagas disease: insights from hierarchical modeling. *PLoS Negl Trop Dis*. 2022;16:e0010612.

220 Verani JR, Seitz A, Gilman RH, et al. Geographic variation in the sensitivity of recombinant antigen-based rapid tests for chronic Trypanosoma cruzi infection. *Am J Trop Med Hyg*. 2009;80:410–415.

221 Barfield CA, Barney RS, Crudder CH, et al. A highly sensitive rapid diagnostic test for Chagas disease that utilizes a recombinant *Trypanosoma cruzi* antigen. *IEEE Trans Biomed Eng*. 2011;58:814–817.

222 Gabaldón-Figueira JC, Skjefte M, Longhi S, et al. Practical diagnostic algorithms for Chagas disease: a focus on low resource settings. *Expert Rev Anti Infect Ther*. 2023;21:1287–1299.

223 Miranda-Arboleda AF, Zaidel EJ, Marcus R, et al. Roadblocks in Chagas disease care in endemic and nonendemic countries: Argentina, Colombia, Spain, and the United States. The NET-Heart project. *PLoS Negl Trop Dis*. 2021;15:e0009954.

224 Echeverría LE, Marcus R, Novick G, et al. WHF IASC roadmap on Chagas disease. *Glob Heart*. 2020;15:26.

225 Olivo Freites C, Sy H, Gharamti A, et al. Chronic chagas disease-the potential role of reinfections in cardiomyopathy pathogenesis. *Curr Heart Fail Rep*. 2022;19:279–289.

226 Bosch-Nicolau P, Fernández ML, Sulleiro E, et al. Efficacy of three benznidazole dosing strategies for adults living with chronic Chagas disease (MULTIBENZ): an international, randomised, double-blind, phase 2b trial. *Lancet Infect Dis*. 2024;24:386–394.

227 Padilla AM, Wang W, Akama T, et al. Discovery of an orally active benzoxaborole prodrug effective in the treatment of Chagas disease in non-human primates. *Nat Microbiol*. 2022;7:1536–1546.

228 Tarleton RL. Effective drug discovery in Chagas disease. *Trends Parasitol*. 2023;39:423–431.

229 Sánchez-Valdéz FJ, Padilla A, Wang W, Orr D, Tarleton RL. Spontaneous dormancy protects Trypanosoma cruzi during extended drug exposure. *Elife*. 2018;7. https://doi.org/10.7554/eLife.34039.

230 Bustamante JM, Sanchez-Valdez F, Padilla AM, White B, Wang W, Tarleton RL. A modified drug regimen clears active and dormant trypanosomes in mouse models of Chagas disease. *Sci Transl Med*. 2020;12. https://doi.org/10.1126/scitranslmed.abb7656.