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Reservoir host competence and the role of domestic and commensal hosts in the transmission of *Trypanosoma cruzi*

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ABSTRACT

We review the epidemiological role of domestic and commensal hosts of *Trypanosoma cruzi* using a quantitative approach, and compiled >400 reports on their natural infection. We link the theory underlying simple mathematical models of vector-borne parasite transmission to the types of evidence used for reservoir host identification: mean duration of infectious life; host infection and infectiousness; and host-vector contact. The infectiousness of dogs or cats most frequently exceeded that of humans. The host-feeding patterns of major vectors showed wide variability among and within triatomine species related to their opportunistic behavior and variable ecological, biological and social contexts. The evidence shows that dogs, cats, commensal rodents and domesticated guinea pigs are able to maintain *T. cruzi* in the absence of any other host species. They play key roles as amplifying hosts and sources of *T. cruzi* in many (peri)domestic transmission cycles covering a broad diversity of ecoregions, ecotopes and triatomine species: no other domestic animal plays that role. Dogs comply with the desirable attributes of natural sentinels and sometimes were a point of entry of sylvatic parasite strains. The controversies on the role of cats and other hosts illustrate the issues that hamper assessing the relative importance of reservoir hosts on the basis of fragmentary evidence. We provide various study cases of how eco-epidemiological and genetic-marker evidence helped to unravel transmission cycles and identify the implicated hosts. Keeping dogs, cats and rodents out of human sleeping quarters and reducing their exposure to triatomine bugs are predicted to strongly reduce transmission risks.

1. Introduction

Multihost pathogen transmission systems include many zoonoses with complex dynamics that challenge disease control and prevention efforts (Dobson, 2004). Having a multiplicity of hosts may favor pathogen persistence (maintenance), high pathogen abundance (amplification) or reduce both of them (the dilution effect) (Begon, 2008).

Trypanosoma cruzi (Kinetoplastida: Trypanosomatidae), the etiological agent of Chagas disease, is a relevant example of a vector-borne multihost pathogen and a serious cause of morbidity and mortality affecting 6–9 million people (WHO, 2015). *T. cruzi* is composed of highly heterogeneous populations classified into six Discrete Typing Units (DTUs): TcI–TcVI (Miles et al., 2009; Zingales et al., 2012). TcI is widespread through the Americas in association with *Didelphis* opossums, and predominates in domestic transmission cycles occurring north of the Amazon basin. TcIII and TcIV mainly circulate in sylvatic transmission cycles whereas TcII, TcV and TVI predominate in domestic habitats from the Southern Cone of South America. All DTUs can cause human infection and disease (Miles et al., 2009; Zingales et al., 2012). The six DTUs are currently associated with distinct ecological niches, and this has implications for understanding the eco-epidemiology of *T. cruzi* and developing improved disease control and surveillance strategies (Miles et al., 2009). A bat-associated genotype (TcBat) genetically close to TcI was reported (Marcili et al., 2009a).

All mammals are considered susceptible to *T. cruzi* whereas birds and other vertebrates are refractory to infection (WHO, 2002). Opossums, armadillos and rodents are major sylvatic reservoir hosts, whereas humans, dogs, cats and commensal (synanthropic) rodents are the main hosts in domestic or peridomestic (i.e., (peri)domestic) habitats (Jansen and Roque, 2010; Minter, 1976a; Noireau et al., 2009; WHO, 2002). *Trypanosoma rangeli*, another Trypanosomatidae infecting humans, dogs and other mammals

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through the bite (salivaria transmission) of triatomine bugs of the genus *Rhodnius*, is considered non-pathogenic for mammals and pathogenic for triatomines (Pifano, 1973; Pineda et al., 2011; Ramírez et al., 2013; Vallejo et al., 2009).

T. cruzi infection is typically acquired through skin contamination with feces from infected triatomine bugs (stercorarian transmission), although the infection may occur through additional routes, including: (1) ingestion of infected bugs; (2) ingestion of food and beverages contaminated with feces of infected triatomines or with urine or feces of infected opossums or other mammals; (3) licking fur contaminated with infected bug feces or infected blood; (4) ingestion of domestic flies or cockroaches that had recently ingested fresh feces from infected triatomines; (5) ingestion of infected mammals (or infected raw meat) or unprotected contact with their blood; (6) congenital transmission or through maternal milk; (7) sexual or other direct contact with infected body secretions; and (8) blood transfusion and organ transplantation. Routes 1–4 are partially triatomine- related; routes 1 and 3–4 are restricted to non-human hosts, and routes 1–5 have an oral point of entry (Hoare, 1972; Minter, 1976a; Zeledón, 1974).

Some species of Triatominae which adapted to live in human dwellings or its annexes acquired public health relevance (WHO, 2002). The list is headed by *Triatoma infestans*, *Rhodnius prolixus*, *Panstrongylus megistus*, *Triatoma dimidiata* and *Triatoma brasiliensis*, but several other species occasionally invade homes and may transmit *T. cruzi* to humans. Disease control strategies traditionally focused on preventing parasite transmission by recurrent house spraying of residual insecticides to suppress bug infestations; screening blood donors, and by treating acute or subacute cases and infected infants born to infected mothers (WHO, 2002).

This review was initially motivated by the following statement from a highly influential, widely cited publication of the World Health Organization (WHO, 2002): "The natural reservoirs of *T. cruzi* are those mammals – domestic, synanthropic, and wild –, including humans, that are naturally infected by the parasite. Such reservoirs play an important part in the maintenance of, and interaction between, the domestic and wild cycles of Chagas disease" (p. 56). The underlying notions that all host species found to be infected are reservoir hosts and are important for pathogen maintenance are misleading; disagrees with the modern consensus in the field (Sections 2 and 3), and affects both risk assessment and decision making.

This manuscript provides a critical appraisal of the epidemiological role of domestic and commensal hosts of *T. cruzi* using a quantitative approach. As a guiding principle we sought to establish the links among triatomine and various domestic host species and follow the transfer of parasite DTUs. After summarizing current definitions of reservoir host, we link the theory underlying simple mathematical models of vector-borne parasite transmission to the types of evidence used for reservoir host identification. We use domestic dogs as an in-depth study case, partly because of their relevance; there is more experimental and epidemiological information on dogs than on any other natural host (except humans), and partly because of our own experience. We document the roles of dogs, cats, commensal rodents and domesticated guinea pigs as amplifying hosts, sources and domestic risk factors, and use the controversies on their roles to illustrate some of the issues involved. We provide various examples of how molecular epidemiology evidence may contribute to unravel transmission cycles and identify the putative reservoir hosts by "contact tracing". This review excludes other important wild reservoir hosts of *T. cruzi* (e.g., opossums, non-domesticated guinea pigs) that may live in close proximity to humans, including feral pigs, feral goats and bats. A thorough understanding of the role of domestic and commensal reservoir hosts may contribute to the design and implementation of innovative Chagas disease control strategies that target infectious host species and individuals, and may prevent, reduce or suppress parasite transmission in more cost-effective ways.

2. General framework: definitions of reservoir hosts

The plethora of terminology growing over recent decades has led to frequent confusions. Ashford (1996, 2003) defined a reservoir of infection as an "ecological system in which the infectious agent survives indefinitely", and classified reservoirs into different types. A reservoir host is responsible for the long-term maintenance of a population of infectious agents. Incidental hosts (also termed accidental) are irrelevant to long-term parasite persistence, but occasionally may be responsible for some transmission and even become secondary reservoir hosts. Although not an essential component, "a liaison host is one that becomes infected and brings the agent to a situation where it can be transmitted to humans" (i.e., a bridge host) (Ashford 1996, 2003).

By definition a parasite species that persists in a reservoir host population must have a basic reproduction number (R_0) greater than 1 (Anderson and May, 1991). For a microparasitic infection, R_0 is defined as the average number of secondary cases arising from a primary case in a susceptible population. It measures the risk that an outbreak will occur if the pathogen is introduced; the initial exponential increase in the number of infected hosts, and the amount of effort required to eliminate the infection (Hartemink et al., 2008). A primary reservoir host can maintain endemic transmission of a pathogen ($R_0 > 1$) in the absence of any other host species, and the parasite can persist indefinitely in this host alone (Quinnell and Courtenay, 2009; Reithinger and Davies, 1999). Secondary reservoir hosts can transmit infection and increase R_0 but cannot maintain parasite transmission in the absence of the primary host(s). Incidental hosts do not modify R_0. Sustained control measures that suppress or block parasite transmission from the primary reservoir host can eliminate the pathogen by reducing R_0 below 1, whereas control actions directed at secondary reservoir hosts would reduce R_0 but not lead to elimination. Actions targeting incidental hosts are ineffectual.

Haydon et al. (2002) proposed "that a reservoir be defined as one or more epidemiologically connected populations or environments in which the pathogen can be permanently maintained and from which infection is transmitted to the defined target population", i.e., the one that is of interest to our purposes. A source is any population that transmits infection directly to the target population. Maintenance populations of a single host species are capable of maintaining a pathogen indefinitely (i.e., they are larger than the critical community size). The populations in a reservoir constitute a maintenance community which may include the target population, maintenance and non-maintenance populations, non-essential hosts, and vector species. Chaves et al. (2007) proposed that "reservoirs are those species that have a dynamic feedback to the other hosts through pathogen transmission by the vector" (i.e., sources), whereas incidental hosts lacking such feedback should be considered sinks.

Begon (2008) described a "competent reservoir host as one capable of sustaining a pathogen ($R_0 > 1$, long term) ", and further identified that a host capable of passing on the infection may not be competent because of the dependence of R_0 on the abundance of susceptible hosts and on the average life expectancy of infectious hosts (determined by death or recovery). In a two-host species system with interspecific transmission, spillover events from the more competent host to the incompetent host contribute to overall pathogen maintenance and may cause a substantial epidemic and further spillovers before dying out; this means that transient behaviors are also relevant and may lead to emerging infectious disease outbreaks (Fenton and Pedersen, 2005). A case in point

is sylvatic plague (caused by the bacterium *Yersinia pestis*), which shows periods of enzootic transmission and epizootic outbreaks involving different small mammal species in the southwestern USA (Gage and Kosoy, 2005). The enzootic and epizootic hosts are usually denominated maintenance and amplifying hosts, respectively, to emphasize their distinctive roles for pathogen persistence and multiplication.

3. Identification of reservoir hosts in vector-borne diseases

The leishmaniases illustrate a case where the identification of reservoir hosts has proved especially difficult and controversial. The topic is as complex as the variety of *Leishmania* and sandfly species involved (Ashford, 2000). The debate ranges from the putative reservoir hosts of *Leishmania tropica* to random guesses at the reservoir hosts of Old World *Leishmania*. The criteria used for reservoir host identification included: a positive correlation between the occurrence of human infection with a defined *Leishmania* species and reservoir host presence or density; concomitant variation in the prevalence (or risk) of infection in humans and in the reservoir host(s); co-occurrence of the same parasite strain(s) in reservoir hosts and humans; presence of parasite DNA; low pathogenicity in the reservoir host; and host infection prevalence greater than 20%. Some of these criteria were objected on various grounds (e.g., Ashford, 1996; Chaves et al., 2007; Haydon et al., 2002; Quinnell and Courtenay, 2009; Reithinger and Davies, 1999). Intervention trials are needed to provide concluding evidence on the role of reservoir hosts, but they may be costly, unfeasible or unwarranted. The next option for reservoir host identification depends on a thorough ecological understanding based on key empirical data, and developing mathematical models tailored to the study system.

An extension of the Ross-Macdonald model for human malaria (Dye, 1992) was used to describe the dynamics of a vector-transmitted disease (Human African Trypanosomiasis, HAT) with two vertebrate hosts and one vector species (Rogers, 1988). At equilibrium, R_0 varied with: the relative abundance of vectors to hosts from each species (m); the prevalence of infection in vectors and hosts (infection); the biting rate on each host species (host-vector contact rate, a, the host blood index divided by the feeding interval); the probability that a feeding on an infected host produced a patent infection in the vector (host infectiousness, (c); duration of the infectious period ($1/r$); and other factors. For HAT caused by *Trypanosoma brucei gambiense* (traditionally considered an anthroponosis in western Africa), pathogen persistence in certain scenarios depended on having a non-human reservoir host. Another approach (the next-generation matrix) reached the same conclusion (Funk et al., 2013). Although some studies have shown that domestic and wild mammals may harbor *T. b. gambiense*, the empirical evidence on their reservoir host competence is scant.

Mather et al. (1989) introduced the concept of "reservoir potential" to describe the relative contribution of rodent host species to the horizontal infection of ticks (*Ixodes damnini*) with the Lyme disease spirochete *Borrelia burgdorferi*. The authors used rodent species-specific data on the prevalence of infection, infectiousness, density, and infestation with larval stages to conclude that white-footed mice (*Peromyscus leucopus*) were the most important small mammal reservoir in coastal Massachusetts. One of the components of reservoir potential, later called "realized reservoir competence", was defined as the product between the prevalence of host infection and host infectiousness (Brunner et al., 2008). More in line with metapopulation theory, "reservoir capacity" was recently defined as a weighted measure of the potential of a structured host metapopulation to support the long-term persistence of a pathogen in the absence of external imports (Viana et al., 2014).

For Chagas disease, the seminal reviews of Minter (1976a,b) established a qualitative hierarchy among hosts of *T. cruzi* based on the existing data of the prevalence of host infection (by serodiagnosis or xenodiagnosis), and the association between bloodmeal sources and bug infection in multiple transmission cycles. Related to the notion of reservoir host competence described above, we estimated a weighted average probability of bug infection after a single feed (P_a) on any human or dog from Amamá, a hyperendemic rural village of northwest Argentina. For each host population, P_a is the combined product of the age-specific proportions of seropositive to *T. cruzi*, of seropositive individuals with positive xenodiagnosis, and of infected third-fourth instar nymphs in individuals with positive xenodiagnosis, weighted by age group (Gürtler et al., 1996a). The P_a of an uninfected bug fed randomly on any dog was 50 times higher than that of an uninfected bug fed on any human.

Another improved index of the contribution of each domestic host population (dogs, cats, humans) to bug infection was derived from the product of three numbers specific to those host and vector populations: (1) the fraction of bugs that have a blood meal from the particular host population; (2) the prevalence of xenodiagnosis-positive hosts in each host population; and (3) the infectiousness of each host population to an uninfected bug in a single blood meal (Gürtler et al., 2007a). Dogs and cats contributed, respectively, 13.9 and 4.8 times as much as humans to infection of domestic bugs. In the next sections we review the published data on the domestic and commensal hosts of *T. cruzi* and assess their reservoir host competence in the light of a chain of processes: host susceptibility, infection and survival; host infectiousness; and host-vector contact.

4. Domestic dogs

4.1. Course of infection

The natural course of host infection is a determinant factor in the transmission dynamics of *T. cruzi* and other pathogens. Although all mammalian hosts are considered susceptible to *T. cruzi*, some degree of age-related resistance is generally accepted (Barr, 2009; Desquesnes and de Lana, 2010). Detailed knowledge of the course of *T. cruzi* infection in non- human hosts is mainly restricted to dogs (and rodents) because of their advantage as an experimental model of human Chagas disease (Barr, 2009; Desquesnes and de Lana, 2010; Guedes et al., 2002; Marsden and Hagstrom, 1968). Pathological findings are parasite strain-dependent; detailed accounts may be found elsewhere (Barr, 2009; Desquesnes and de Lana, 2010).

A typical course of a primary infection with *T. cruzi* in dogs includes an initial acute phase with a short latent period of 1 and 2 weeks for parasitological and serological conversion, respectively (Lauricella et al., 1986; Machado et al., 2001). Patent parasitemia appears as early as 3 days post- infection and disappears one month later, whereas specific antibodies to *T. cruzi* appear 2–3 weeks post-infection. *T. cruzi* was isolated from saliva and urine of puppies infected with massive infectious doses (Marsden and Hagstrom, 1968). Mortality from acute myocarditis may be very high in young dogs aged less than 6–12 months (Barr, 2009; Kjos et al., 2008). Dog mortality depends on the virulence of parasite strains, size of inoculum, route of infection, and host age (Marsden and Hagstrom, 1968; Barr, 2009; Desquesnes and de Lana, 2010). Mongrel dogs inoculated with a small infectious dose underwent a mild infection with no mortality or electrocardiographic alterations attributable to *T. cruzi* (Lauricella et al., 1986). Acute infections in sub-adult or adult dogs are milder and mostly unapparent. The life-long chronic phase shows a time-dependent decline of infectiousness and persisting levels specific antibodies detectable by routine serodiagnostic methods. Some dogs develop a chronic myocarditis that may lead to sudden death.

How much these results inform us of natural infections is hard to elucidate. Early observations by Salvador Mazza and other researchers (Mazza and Jörg, 1936; Mazza and Lobos, 1937; Mazza, 1934) documented both fatal cases and uncomplicated acute infections with *T. cruzi* in well-nourished mongrel dogs aged less than 3 months, often with no pathognomonic signs of clinical disease. Under substantial risk levels, all surveyed dogs were seropositive to *T. cruzi* by the age of 4–5 years (Gürtler et al., 1996a, 1986a) suggesting little or no refractoriness to infection. Spontaneous serorecovery (i.e., reversal from seropositive to seronegative) was exceptionally reported in dogs (Castañera et al., 1998) and humans (Zeledón et al., 1988). Electrocardiographic surveys of infected dogs from endemic rural areas evidenced either a very low frequency of abnormalities or unspecific ones (Lauricella et al., 1989; Ruiz et al., 1985) or significant cardiac alterations (Cruz-Chan et al., 2009). Numerous fatal cases of young dogs (mainly pure-bred) were recorded in veterinary clinics from southern USA (Barr, 2009; Kjos et al., 2008; Williams et al., 1977). Infected dogs diagnosed at a later age survive longer than those which presumably acquired the infection at an earlier age (Barr, 2009).

This apparent discrepancy between field observations may perhaps be attributed to: the availability of veterinary clinics and a reporting bias; dog breed (mongrel versus pure-bred); parasite strain; and poverty-related host malnutrition (see Section 4.3). Mongrel dogs from traditionally endemic rural areas are the offspring of parents that survived the infection (a process repeated over many generations), and therefore may be phenotypically or genetically more resistant to infection. In addition to typical stercorarian transmission, triatomine consumption by dogs was substantial (12–27%) in closed experimental huts housing untreated dogs (Gürtler et al., 2009b; Reithinger et al., 2006). Oral infections with *T. cruzi* may account for many canine cases, especially in settings where infected sylvatic bugs frequently invade house premises. Naturally-infected bugs may carry up to 30,000 trypomastigotes per μl of rectal contents (Giojalas et al., 1990): dogs preying upon them may develop virulent infections as in food-borne outbreaks of human Chagas disease. The probability of host infection through ingestion of *T. cruzi*-infected bugs (0.177) in sylvatic mammals (Kribs-Zaleta, 2010) exceeded the estimated probability of human infection through stercorarian transmission (Nouvellet et al., 2013; Rabinovich et al., 1990) by several orders of magnitude.

4.2. Prevalence of infection

This review is based on electronic searches in MEDLINE/PubMed by using the search terms “dogs”, “natural”, “infection”, “cruzi”, “Chagas”, “presence”, “reservoir”, “host”, and “occurrence” (last accessed on May 15, 2015); in Google Scholar, using the search terms “dogs”, “cruzi” and each country name; in citations found in broad-ranging reviews or book chapters and monographs (including Barretto, 1985, 1964; Coura and Dias, 2009; Deane, 1964; Jansen and Roque, 2010; Minter, 1976a; Noireau et al., 2009; Dias, 2000) and in the authors’ collections. Additional searches were performed in the electronic database BibTri (http://bibtri.com.ar/) using the search terms “dogs” and “cats”. The same procedures were conducted using the search terms “cats” and “rodents” instead of “dogs”. Additional searches for “goats” and “cruzi”; “pigs” or “swine” and “cruzi”; and “domestic mammals” and “cruzi” and/or “infection” and/or “Chagas” were done. No restrictions to language, calendar date, study size or diagnostic method were set. Information appearing in the grey literature was specifically sought and included after checking the original material. A small fraction of manuscripts could not be accessed in print or electronically, and thus were excluded from this review.

Supplementary Table 1 compiles the published reports of dogs naturally infected with *T. cruzi*. Infected dogs have been reported from the USA to southern Argentina and Chile, including areas with only sylvatic transmission cycles (e.g., USA, West Indies and the Amazon basin). All six *T. cruzi* DTUs were identified in dogs (Cardinal et al., 2008; Ramírez et al., 2013; Roellig et al., 2008). Prevalence rates of dog infection greater than 50% were recorded in several areas infested by *T. infestans* and *R. prolixus*, sometimes reaching or exceeding the local human infection rates, but dog prevalence more typically varied between 10% and 30%. Direct comparisons between reported prevalence rates are often misleading because of large variations among diagnostic methods and their performance (Supplementary Text 2), and in the local history of vector control actions. Detection of non-acute infections with *T. cruzi* is best accomplished through validated serological methods (Lauricella et al., 1998). Prevalence surveys frequently used convenience sampling designs, had limited sample sizes, and lacked clear definitions of the study population, sampling coverage, and selection criteria.

The absence of spontaneous (sero) recovery after the primary infection with *T. cruzi* implies that the age-specific seroprevalence rates of infection reflect the cumulative risk of infection over the life course (Fig. 1A). These data may be used to estimate the force of infection (i.e., the instantaneous rate of *per capita* conversion from negative to positive) through a susceptible-infected (SI) transmission model (Anderson and May, 1991). The force of *T. cruzi* infection in dogs from two highly-infested rural areas in northwest Argentina varied from 43.2 to 72.7 per 100 dog-years, suggesting an average age at primary infection of 5–6 months (see Supplementary Fig. 4 in Gürtler et al., 2007a, 2005). Age-prevalence curves of dog infection increased with infected-bug density, differed substantially between population subgroups, and reflected the intensity of previous vector control actions (Cardinal et al., 2007, 2014).

4.3. Host infectiousness

The intensity of host infectiousness to the vector can be measured by xenodiagnosis in at least three partially related forms: (1) the proportion of all tested hosts that are xenodiagnosis-positive (infectious); (2) the proportion of hosts seropositive for *T. cruzi* that are infectious to the vector; and (3) the proportion of uninfected vectors that become infected after a replete blood meal on an infected host (i.e., denominated host infectiousness or *c* above). Xenodiagnosis-positive dogs were also successfully identified by quantitative real-time PCR (qPCR), and the concentration of *T. cruzi* DNA correlated closely with dog infectiousness (Enriquez et al., 2014). In systematic surveys of well-defined populations, the prevalence of xenodiagnosis-positive individuals among domestic dogs (28.6%) and cats (19.7%) exceeded that in humans (5.7%) in southeast Brazil (Freitas, 1950), and a similar ranking was often recorded in areas infested by *R. prolixus*, *T. dimidiata* and *T. infestans* (Gürtler et al., 1996a; Pifano, 1973; Zeledon et al., 1975).

Table 1 shows the published reports of dog infectiousness as determined by xenodiagnosis. Overall, the median percentage of infectious dogs was 16% (Q1–Q3, 8–41%); whereas on average, 66% (range, 21–86%) of *T. cruzi*-seropositive dogs were infectious to *T. infestans*. The median percentage of xenodiagnostic bugs (bug instars and species combined) that became infected after feeding on a seropositive dog was 53% (range, 29–56%). In contrast, *T. cruzi*-seropositive human hosts infected 1.9–3.1% of xenodiagnostic bugs (using third–fourth instar nymphs) to 13.6–27.6% (fifth instars), and up to 30–50% of seropositive humans were xenodiagnosis-positive when a large number of bugs was used (Cerisola et al., 1974 Pifano, 1973; references in Gürtler et al., 1996a). Measuring host infectiousness through xenodiagnosis implicitly carries various components related to vector competence which are absent

Table 1
Infectiousness to the vector of dogs naturally infected with *T. cruzi*. This table only includes publications based on at least 10 hosts examined for infection.

Country/locality	Vector species (number nymphs/stage)	Percentage of infectious hosts (no. infectious/no. examined)	Percentage of bugs infected (no. infected/no. examined)	Reference
Argentina, Chaco, Resistencia	*Triatoma infestans* (8 nymphs III or IV)	23.6 (63/267)	NR	Mayer and Alcaraz (1954)
Argentina, Santiago del Estero (SE), Amamá, 1982	*T. infestans* (20 nymphs III or IV)	75.0 (42/56)	NR	Gürtler et al., (1986a)
Argentina, SE, Guanaco Muerto	*T. infestans* (20 nymphs III or IV)	68.0 (17/25)	NR	Wisnivesky-Colli et al., (1985)
Argentina, SE, La Invernada	*T. infestans* (20 nymphs III or IV)	46.2 (18/39)	NR	Wisnivesky-Colli et al. (1985)
Argentina, Córdoba, Cruz del Eje	*T. infestans* (20 nymphs III)	68.0 (17/25)	NR	Ruiz et al. (1985)
Argentina, SE, Amamá 1984	*T. infestans* (10–20 nymphs III or IV)	86.7 (85/98)	62.3 (427/685)	Gürtler et al. (1986b)
Argentina, SE, Rio Hondo	*T. infestans* (20 nymphs)	19.4 (66/340)	NR	Lauricella et al. (1989)
Argentina, SE, Amamá 1984, 1986, 1987	*T. infestans* (10-20 nymphs III or IV)	87.0 (40/46) 86.5 (45/52) 77.2 (17/22)	55.8 (378/678) 52.1 (383/735) 53.1 (196/369)	Gürtler et al. (1992b)
Argentina, SE, Trinidad & Mercedes, 1988	*T. infestans* (20 nymphs III or IV)	41.2 (28/68)	NR	Gürtler et al. (1993)
Argentina, SE, Amamá, 1992	*T. infestans* (10-20 nymphs III or IV)	85.3 (29/34)[a]	48.7 (197/610)	Gürtler et al. (1996a)
Argentina, SE, Amamá, 1990	*T. infestans* (20 nymphs III)	69.0 (20/29)	27.8 (103/371)	Petersen et al. (2001)
Argentina, Chaco, Tres Estacas	*T. infestans* (30 nymphs III-V)	15.1 (16/106)	NR	Diosque et al. (2004)
Argentina, SE, Trinidad & Mercedes, 1988-1989	*T. infestans* (10-20 nymphs III)	65.8 (25/38)[a]	29.5 (186/630)	Gürtler et al. (2007a)
Argentina, SE, Amamá and other 37 villages	*T. infestans* (20-30 nymphs III-IV)	71.4 (35/49)[a]	54.4 (33/612)	Cardinal et al. (2008)
Argentina, Chaco, Pampa del Indio	*T. infestans* (10-20 nymphs IV)	82.7 (43/52)[a]	NR	Enriquez et al. (2013)
Argentina, Chaco, Pampa del Indio	*T. infestans* (10-20 nymphs IV)	86.4 (38/44)[a,b]	48.0, n= NR	Enriquez et al. (2014)
Bolivia, Cochabamba, Colcapirhua	ND	6.1 (2/33)	ND	Román (1947)
Bolivia, Potosí, Vichacla	ND	12.8 (2/17)	ND	Román (1947)
Bolivia, Santa Cruz, Porongo	*T. infestans* (7 nymphs III)	23.4 (29/124)	ND	De Muynck et al. (1978)
Bolivia, Cochabambita & Guapomocito	*T. infestans* (14 nymphs III)	7.7 (3/39)	NR	Brenière et al. (1998)
Brazil, Minas Gerais, Jaboticatubas	*T. infestans, T. vitticeps or P. megistus* (5 nymphs)	22.7 (5/22)	ND	Martins et al. (1945)
Brazil, Sao Paulo, Cassia dos Coqueiros	ND	28.6 (161/563)	ND	Freitas (1950)
Brazil, Goiás, Montevidiu	ND	5.9 (1/17)	ND	Freitas and Mendonça (1951)
Brazil, Campo Florido	*T. infestans* (5 nymphs)	7.8 (8/102)	NR	Freitas et al. (1952)
Brazil, São Paulo, Ribeirao Preto	*T. infestans*	0 (0/18)	ND	Siqueira et al. (1957)
Brazil, Minas Gerais, Campo Florido	ND	3.0 (1/33)	ND	de Rocha and de Siqueira (1958)
Brazil, Ceará Crato, Barbalha	ND	2.8 (2/72)	ND	Alencar et al. (1963)
Brazil, São Paulo, Guaíra	ND	0 (0/34)	ND	Forattini et al. (1971)
Brazil, Ceará, Russas	ND	14.7 (99/674)	ND	Alencar et al. (1974)
Brazil, Castro Alves	*T. infestans* (10 nymphs V)	18.5 (5/27)	NR	Mott et al. (1978)
Brazil, São Paulo, São Joao de Boa Vista	*T. infestans* (10 nymphs IV or V)	0.3 (2/613)	NR	Forattini et al. (1978)
Brazil, Bahia, Riacho da Santana	*T. infestans* or *R. prolixus* (5 nymphs V)	19.2 (5/26)	NR	Barrett et al. (1979)
Brazil, Minas Gerais, Frutal	NR	0.2 (1/509)	NR	Forattini et al. (1983)
Brazil, São Paulo, Minas Gerais	ND	0.2 (ND)	ND	Barretto (1985)
Chile, Huasco, Domeyco	ND	34.8 (16/46)	ND	Gasic and Bertin (1939)
Chile, previous data	ND	20.6 (38/184)	ND	Gasic, (1943)
Chile,Atacama, Altamira	ND	15.3 (2/13)	ND	Whiting (1946)
Chile, summary up to 1948 (dogs and cats pooled)	ND	13.4 (426/3182)	ND	Neghme et al. (1949)
Chile, summary	ND	9.1 (302/3321)	ND	Neghme and Schenone (1963)
Chile, Santiago, Colina	ND	2.0 (2/98)	ND	Perez et al. (1970)
Chile, summary 1939-1969	*T. infestans* (7 nymphs III)	8.8 (307/3492)	NR	Schenone (1971)
Chile, summary 1929-1972	*T. infestans* (7 nymphs III)	8.3 (313/3579)	NR	Schenone et al. (1972)
Chile, Santiago, Colina & Caleu	*T. infestans* (10 nymphs III)	9.3 (8/86)	NR	Rojas et al. (1973)
Chile, various regions, 14 localities	ND	4.1 (45/1101)	ND	Schenone et al. (1978)
Colombia, Santander, Tibú	ND	14.3 (3/21)	ND	Gutierrez (1962)
Costa Rica, San Rafael Ojo de Agua	*T. dimidiata* or *T. infestans or R. prolixus* or *R. neglectus* (10 nymphs IV-V)	9.9 (25/253)	NR	Zeledón et al. (1975)
Costa Rica, Central Valley	*R. prolixus* (20 nymphs IV or V)	21.4 (3/14)[a]	NR	Montenegro et al. (2002)
El Salvador	ND	5.1 (21/413)	ND	Cedillos et al. (1976)
Mexico, Morelos	*Triatoma pallidipennis* (5 nymphs V)	0 (0/49)	ND	Salazar-Schettino et al. (1997)
Paraguay	ND	16.0 (4/25)	ND	Canese (1978)
Perú, Arequipa, Vitor, Tambo	ND	38.1 (16/42)	ND	Clark and Dunn (1932)
Perú, Moyobamba	*T. infestans* or *R. prolixus* or *P. herreri* (8 nymphs II-V)	3.7 (1/27)	NR	Herrer (1956)
Perú, Arequipa, Majes, Moquegua	ND	10.6 (12/113)	ND	Cornejo et al. (1963)
Perú, Arequipa	ND	25.2 (28/111)	ND	Naquira et al. (1972)
Venezuela, Carabobo, Valle de los Naranjos	*R. prolixus* and *T. pallidipennis* (20 and 6 nymphs IV of each)	36.8 (14/38)	ND	Pifano (1973)
Venezuela, Cojedes, 8 localities (includes cats)	*R. prolixus* (10 nymphs IV)	19.4 (25/129)	ND	Tonn et al. (1978)

ND, no data; NR, not reported.
[a] Only seropositive animals were examined.
[b] Only animals aged ≥1 year were reported.

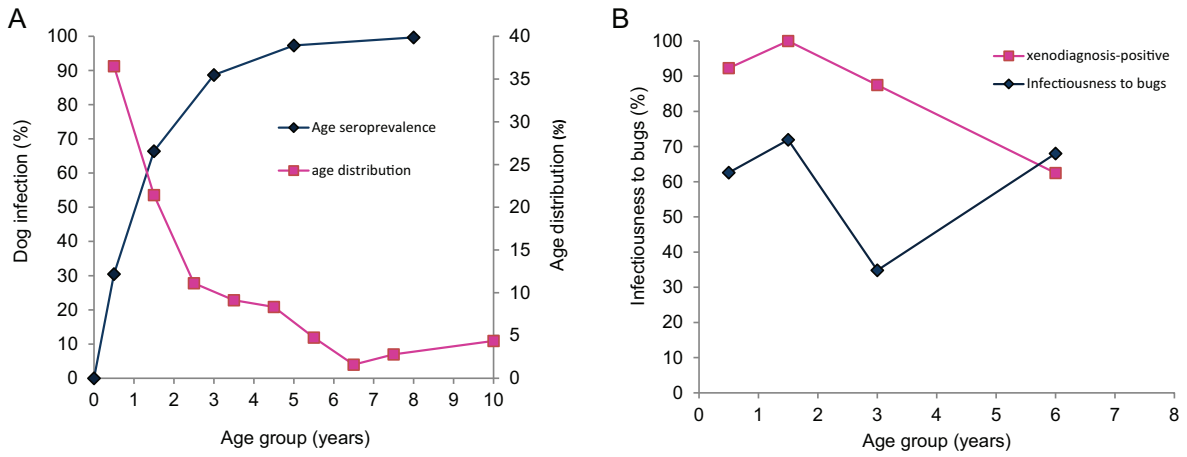

Fig. 1. (A) Age-specific seroprevalence of dog infection with *T. cruzi* as predicted by a susceptible-infected transmission model, and a typical age structure of the dog population in Amamá and neighboring villages. (B) Observed age-specific prevalence of xenodiagnosis-positive dogs among seropositives, and percentage of xenodiagnostic bugs infected with *T. cruzi* (data from Gürtler et al., 1996a).

in hemoculture and qPCR (Supplementary Text 2). The probability of bug infection after feeding on an infected host is crucially related to bloodmeal size, which varies among bug stages, duration of exposure to the host and other factors (reviewed in Gürtler et al., 1996a). For example, the pioneering xenodiagnostic surveys of dogs conducted in Brazil (Freitas, 1950; Freitas et al., 1952; Martins et al., 1945) and recent ones using hemoculture (5–8 mL of host blood) and/or PCR (Bezerra et al., 2014; Eloy and Lucheis, 2012; Lucheis et al., 2005) documented the frequent occurrence of parasitologically-positive dogs or cats (Table 1). In contrast, dogs seropositive for *T. cruzi* across several areas were hemoculture-negative when smaller amounts (0.2–0.4 mL) of blood were tested (Roque et al., 2008; Xavier et al., 2012; Rocha et al., 2013). Whether the current reservoir competence of dogs across several regions of Brazil is negligible (Jansen and Roque, 2010; Xavier et al., 2012) or not merits further inquiry. A few cross-sectional and longitudinal studies attempted to assess the duration of the infectious period through the relation between host infectiousness and age of dog, on the assumption that age is a surrogate of time since primary host infection. The prevalence of xenodiagnosis-positive dogs and their infectiousness either were age-independent or declined marginally or significantly with age (Fig. 1B) (Enriquez et al., 2014; Gürtler et al., 2007a, 1998b, 1996a, 1992a, 1986b; Lauricella et al., 1989). The potential contribution of pups to bug infection (P_a) was approximately 50% greater than that of the older age groups combined (Gürtler et al., 1996a). These variable patterns were also recorded in experimentally-infected dogs, in which patent parasitemia either disappeared one month post-infection and xenodiagnosis remained negative for 0.5–12 years (Araujo et al., 2002; Machado et al., 2001), or infectiousness persisted over a two-year follow-up (Lauricella et al., 1986). The potential interactions among host age, host genetics (i.e., dog breed), parasite strain, multiclonal infection, infectious dose, health status, and co-infections may account for the various patterns recorded in the field.

Two key features of dog infectiousness include high aggregation at the population level and autocorrelation over time (Enriquez et al., 2014; Gürtler et al., 2007a). A variable fraction of naturally-infected, seropositive dogs consistently failed to produce a patent infection in xenodiagnostic bugs whereas another group of highly infectious dogs were considered potential 'superspreaders' of *T. cruzi* (Gürtler et al., 2007a). This heterogeneity in infectiousness implies that some dogs may contribute disproportionally to the onward transmission of *T. cruzi*. Similarly, human infectiousness is highly heterogeneous: some individuals showed persistently high infectiousness over time whereas others consistently showed intermediate, very low or nil infectiousness when measured by xenodiagnosis or hemoculture (Cerisola et al., 1974; Luz et al., 1994).

Both the intensity and apparent duration of dog infectiousness were inversely correlated to an index of body condition reflecting health and nutritional status in two resource- constrained, endemic rural areas of the Argentine Chaco (Enriquez et al., 2014; Petersen et al., 2001). Domestic dogs almost invariably lacked veterinary supervision and vaccination against virulent canine diseases, and suffered from chronic malnutrition and anemia frequently associated with co-infections and protein-deficient diets. Host conditions varied widely within the same village and even more within the same region depending on local levels of socioeconomic deprivation. Dogs owned by poor households were concomitantly in poor body condition elsewhere (Fung et al., 2014). These aspects most likely influence the average duration of infectious life and dog population turnover (see Section 4.4).

Host exposure to reinfections (i.e., superinfection) is frequently mentioned as a determinant of host infectiousness and pathogenesis. In a preliminary survey we found a positive association between dog infectiousness and the household density of infected bugs that was not verified in subsequent surveys (Enriquez et al., 2014; Gürtler et al., 2007a, 1992b). Comparison of the age-specific infectiousness of *T. cruzi*-seropositive dogs before and 1–2 years after suppression of domestic bug infestations revealed insignificant differences over time (Gürtler et al., 1992b). Similarly, the experimental effects of reinoculations on infectiousness in dogs, monkeys and mice were also slight and transient or nil (Andrade et al., 2006; Bustamante et al., 2007; Machado et al., 2001; Riarte et al., 1995). However, when dogs were inoculated successively with two stocks of *T. cruzi*, both genotypes were recovered from three out of eight dogs and one of the genotypes predominated during the follow-up (Machado et al., 2001).

Parasite DTU was not associated significantly with dog infectiousness in a multivariate analysis that controlled for the effects of host body condition and age (Enriquez et al., 2014). However, a few TcI-infected dogs and cats were non-infectious by xenodiagnosis despite having a moderate parasitemia as determined by qPCR. Experimental evidence of pericardial sequestration of TcI associated with cardiomyopathy and barely detectable peripheral parasitemia were also noted (Miles et al., 2009).

4.4. Host population dynamics

The demography of domestic dog populations is driven by human cultural patterns (Matter and Daniels, 2000), and plays a key role in the rate of recruitment of susceptible hosts (by birth or in-migration) and the dispersal of *T. cruzi*-infected dogs within and between communities. The mean life expectancy of a dog and its average age at primary infection by *T. cruzi* were used to estimate R_0 (8.2) in dogs and cats (5.0) before control interventions (Gürtler et al., 2007a).

The demography of rural and urban dog populations differs in several respects (Matter and Daniels, 2000). Several cross-sectional and longitudinal studies in northern Argentina revealed that the dog-to-human ratio was as high as 1:2–1:3, and the number of dogs per household averaged nearly 3 (Cardinal et al., 2014, 2007; Castañera, 1999; Gürtler et al., 2007a, 1990; Orozco et al., 2013a,b). The dog population size remained stationary or increased gradually as the number of households increased over time. The age structure and sex ratios were highly skewed toward young age classes and males, respectively (Fig. 1A). The median age and mean life expectancy were 3 years. Recruitment occurred across seasons; in- and out-migration from the home villages was not marginal, and annual turnover rates were very high (>25%). Dying dogs were almost immediately replaced by new, usually very young dogs which apparently have greater susceptibility to *T. cruzi* and age-related infectiousness, and may be more attached to domestic premises. Domestic dogs usually were neither supervised nor their movements restrained across several rural areas; they had free access to human sleeping quarters and rested in proximity to their owners, but this was not homogeneous across rural areas within the same region.

Does *T. cruzi* infection impact on the demography of rural dog populations? Despite the virulence of *T. cruzi* in naturally-infected dogs (Section 4.1), theory predicts that a parasite that occurs in most hosts would probably cause mild infections and exert little effects on host population size (De Leo and Dobson, 1996). Two strands of evidence suggest that the overall impact of *T. cruzi* on dog demography would be marginal: (1) Suppression of bug infestations through residual insecticide spraying caused an exponential decline in the prevalence of dog infection (Fig. 2A) consistent with the hypothesis of non-differential dog mortality attributable to *T. cruzi* infection (Gürtler et al., 2007b, 1990), and (2) biannual house-to-house surveys of the dog population during nearly four years revealed a stable abundance and age structure despite the fast removal of *T. cruzi*-infected dogs and their replacement with seronegative dogs (Castañera, 1999). The excess of mortality due to *T. cruzi* may be minor as compared with competing risks of death experienced by unvaccinated dogs with untreated helminth infections and evident malnutrition.

4.5. Host-vector contact

The rate of passage of *T. cruzi* from infected dogs to uninfected triatomines is related to the fraction of blood meals taken on the host (host blood index) and the vectors' blood-feeding rate. The latter has rarely been investigated in the field (reviewed in Gürtler et al., 2014a) and is a key parameter of transmission models. Measuring the temperature-adjusted occurrence of transparent (clear) urine shortly after bug capture provides a widely applicable method for estimating daily feeding rates (Catalá, 1991). For *T. infestans* collected from all (peri)domestic bug habitats in mid-spring, the median feeding interval was 4.1 days in human sleeping quarters and varied widely from 2.8 days in chicken coops to 10.2 days in kitchens (Gürtler et al., 2014b).

The host blood index is measured as the percentage of tested insects with a given bloodmeal source as determined by immunologic or molecular methods. Triatomine bugs make opportunistic feeding choices and therefore their host-feeding patterns tend to reflect the relative abundance and proximity of local hosts combined with host attractiveness and defensive behavior (Gürtler et al., 2014a, 2009a). Seasonal variations in the host-feeding patterns of domestic *T. infestans* were related to changing host resting habits and exposure across seasons (Gürtler et al., 1997).

A recent review of the host-feeding patterns of Triatominae listed >150 studies for defined combinations of bug species, locations and type of bug habitat (Rabinovich et al., 2011). This study emphasized the rich diversity of bloodmeal sources identified within the same triatomine species and region, large differences between study habitats (domestic, peridomestic, and sylvatic) within species, and the major role of host accessibility as a determinant of host choice. The main (peri)domestic hosts of Triatominae were mostly restricted to humans, chickens ("avian hosts"), dogs, cats, and rodents. The finding of (peri)domestic triatomines with blood meals on wild reservoir hosts (opossums and armadillos) is evidence of potential overlapping between sylvatic and (peri)domestic transmission cycles in several study sites (see Sections 4.6, 5.2 and 6.2).

A helpful index of the potential contribution of a reservoir host to bug infection with *T. cruzi* can be derived from the association between bloodmeal source and bug infection (Barretto, 1968), later denominated the infective bloodmeal index (Zárate et al., 1980). Based on this index, dogs, cats, rodents, opossums and humans played a significant role as parasite sources (Minter, 1976a). The infective bloodmeal indices of 1085 domestic *T. infestans* showed that dog-fed bugs had higher indices (49%) than those fed on cats (39%), humans (38%), and chickens (29%) (Gürtler et al., 2007a). The substantial fraction of chicken-fed bugs that were infected with *T. cruzi*, even in early-instar nymphs with unmixed blood meals, indicates that the bugs had previously fed on a highly infectious source that was no longer detectable. These findings and the high frequency of mixed blood meals evidence the large host-feeding mobility of domestic *T. infestans* populations (Gürtler et al., 1997, 1996b; Minter, 1976b; Pizarro and Stevens, 2008).

The infective bloodmeal index may be further refined by additionally considering the infecting *T. cruzi* DTUs and relating them to the DTUs identified in sympatric hosts and vectors. This approach implicated both dogs and humans as sources of TcVI and TcV for *T. infestans* (Fernández et al., 2014; Maffey et al., 2012), but larger sample sizes are needed. The co-occurrence of domestic dogs, cats and (peri)domestic *Triatoma sordida* infected with TcVI, TcV and TcI suggests this secondary vector was partially implicated in (peri)domestic transmission cycles (Maffey et al., 2012; Macchiaverna et al., 2015).

4.6. Dogs as a risk factor

The household presence or number of dogs is a risk factor for domestic infestation by *T. infestans* and *T. dimidiata* as documented by several studies differing in size, location and type of multivariate analysis (Bustamante et al., 2014; Dumonteil et al., 2013; Gurevitz et al., 2011; Gürtler et al., 1992a). Moreover, the presence or number of infected dogs significantly increased the relative odds of domestic bug or human infection with *T. cruzi* across several surveys conducted in Amamá and adjacent rural villages in the dry Argentine Chaco (Gürtler et al., 2005, 1998a, 1998b, 1991). The younger the infected dog the higher the domestic bug infection rate. These results are consistent with (and were predicted from) the high prevalence of infection and age-related infectiousness of dogs, the dog infective bloodmeal index, and the finding of shared parasite DTUs in bugs, dogs and humans (see Sections 4.3, 4.5 and 4.7). The co-occurrence of infected dogs and infected children (acute or

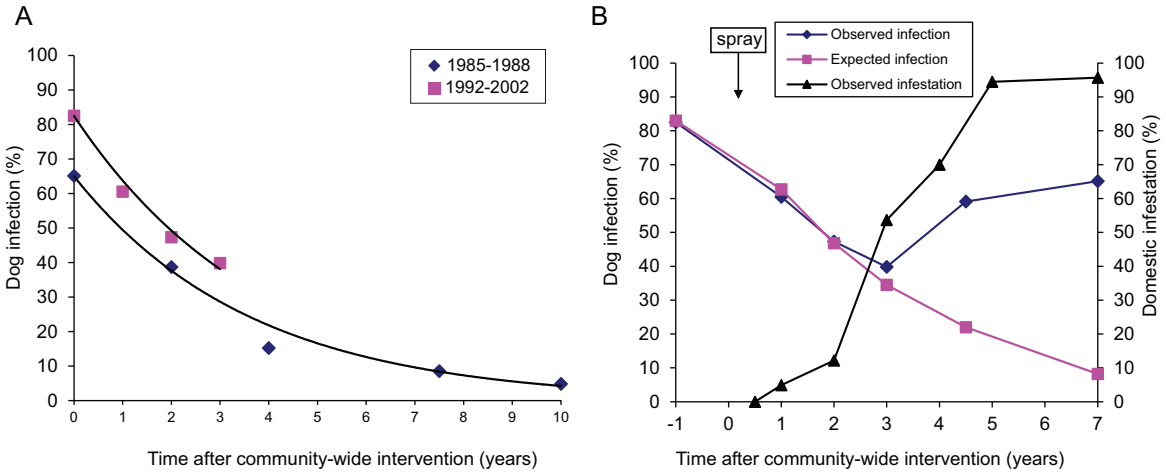

Fig. 2. (A) Prevalence of *T. cruzi* infection in domestic dogs over time following two community-wide campaigns of house spraying with residual insecticides (1985–1988 and 1992–2002), Amamá and neighboring villages (based on Fig. 1B in Gürtler et al., 2007b). Infection prevalence decayed exponentially over years after spraying (x) in 1985–1988 ($y = 82.5 \exp(-0.2578x)$, $R^2 = 0.979$) and 1992–2002 ($y = 65 \exp(-0.2723x)$, $R^2 = 0.967$). R^2 is the coefficient of determination of the exponential decay curve. (B) Observed and predicted prevalence of dog infection with *T. cruzi* and the domestic abundance of *T. infestans* according to years after the first insecticide spraying, 1985–1992.

chronic) was also documented in Argentina, Brazil and Venezuela (Crisante et al., 2006; Mazza, 1936; Mott et al., 1978).

Further evidence for the predicted importance of dogs as reservoir hosts comes from a long-term intervention program based on house spraying with pyrethroid insecticides in Amamá (Gürtler et al., 2007b). The prevalence of *T. cruzi* infection in dogs decayed exponentially at similar rates (25.8–27.2% per year) in the (near) absence of domestic infestations in two study periods across which 1645 dogs were examined for infection (Fig. 2A). The predicted fast decline in dog infection over the initial 2–3 years post-intervention (driven by their fast population turnover, Fig. 2A) was followed by case resurgence in dogs and humans when houses became reinfested and the densities of (infected) domestic *T. infestans* increased (Fig. 2B) (Gürtler et al., 1991, 1990). New cases among dogs preceded the first child case (Gürtler et al., 2007b). Renewed interventions combined with sustained vector surveillance and selective insecticide sprays nearly suppressed house infestations and dropped the dog prevalence of infection from 65% (pre-intervention) to <5% a decade later (Cardinal et al., 2006; Castañera et al., 1998; Gürtler et al., 2007b). Concomitantly, the prevalence of domestic bug infection decreased from 49.1% (pre-intervention) to a mean of 5.6% over the subsequent 12 years, whereas peridomestic bug infection steadily decreased from 5.8% to a mean of 1.3% (Gürtler et al., 2007b).

The new infected dogs detected during this extended surveillance phase were linked to vertical transmission, in-migrant dogs from other infested villages, and more rarely, by transient domestic infestations (Cardinal et al., 2006; Castañera et al., 1998). Therefore, most of the dog infections detected before sustained interventions can be attributed to vector-borne transmission occurring in (peri)domestic habitats. Evidence of oral transmission in dogs was weak or absent during this period, but the intensity of the sympatric sylvatic transmission cycle of *T. cruzi* had declined substantially following increasing deforestation and habitat degradation (Cardinal et al., 2008; Ceballos et al., 2006). The frequency distribution of parasite DTUs in humans, domestic dogs and bugs differed to some extent over two decades, and the degree of overlapping between sylvatic and domestic transmission cycles apparently declined (Cardinal et al., 2008). The appearance of TcIII in a few domestic dogs and one domestic *T. infestans* attested to the introduction of sylvatic DTUs usually found in armadillos and striped skunks (Cardinal et al., 2008; Enriquez et al., 2014; Orozco et al., 2013a,b), and may be related to the widespread habit of feeding dogs with the raw viscera and fresh blood (Cardinal et al., 2014; Deane, 1964). The recent detection of a TcIII-infected human case in the Argentine Chaco is consistent with this chain of evidence (Monje-Rumi et al., 2015). Rare findings of TcIII in dogs were also reported elsewhere (Chapman et al., 1984; Marcili et al., 2009b).

4.7. *Molecular epidemiology of* Trypanosoma cruzi *in the Argentine Chaco*

The distribution of *T. cruzi* DTUs in sympatric domestic hosts and vectors in four study areas from the Argentine Chaco provides a relevant study case of conflicting evidence apparently derived from differing parasite isolation and genotyping methods. Multilocus enzyme electrophoresis of *T. cruzi* stocks isolated through different combinations of xenodiagnosis, mouse subinoculation and culture in monophasic medium suggested a very strong association between TcVI and dogs, and between TcV and humans (occurring in four of five human isolates), with no mixed infections, in Tres Estacas, Chaco province (Diosque et al., 2003). Some 200 km further southwest, in Amamá and adjacent villages (Santiago del Estero province), genotyping of parasite stocks isolated through xenodiagnosis and subsequent culture of bug feces in biphasic medium showed that domestic dogs, cats and *T. infestans* shared the same DTU (TcVI) at most of the study households; the two stocks from humans were TcV, and mixed infections were rare (Cardinal et al., 2008). Using the same methods, a subsequent survey conducted in Pampa del Indio (Chaco province, 350 km northeast of Amamá) corroborated the greater predominance of TcVI in dogs, cats and *T. infestans* relative to TcV, the rarity of mixed infections, and a large fraction of TcVI in domestic triatomines (Enriquez et al., 2013; Maffey et al., 2012).

Several hypothesis were put forward to explain these findings (Fernández et al., 2014): (i) differential DTU selection by human and dogs; (ii) differential DTU amplification of multiclonal infections by existing parasitological methods; (iii) differential tissue tropism of DTUs, and (iv) the existence of two nearly independent transmission cycles mediated by *T. infestans* in (peri)domestic habitats (TcV-humans and TcVI-dogs). The last hypothesis was considered very unlikely in the absence of any known mechanism leading to the stable segregation of sympatric DTUs.

The most recent, largest survey conducted in the same region yielded 115 DTU identifications from PCR-positive human and dog blood samples typed directly by PCR-DNA blotting and hybridization assays (Monje-Rumi et al., 2015): TcV predominated in humans and TcVI in dogs, as in previous studies, but nearly half (40/81) of

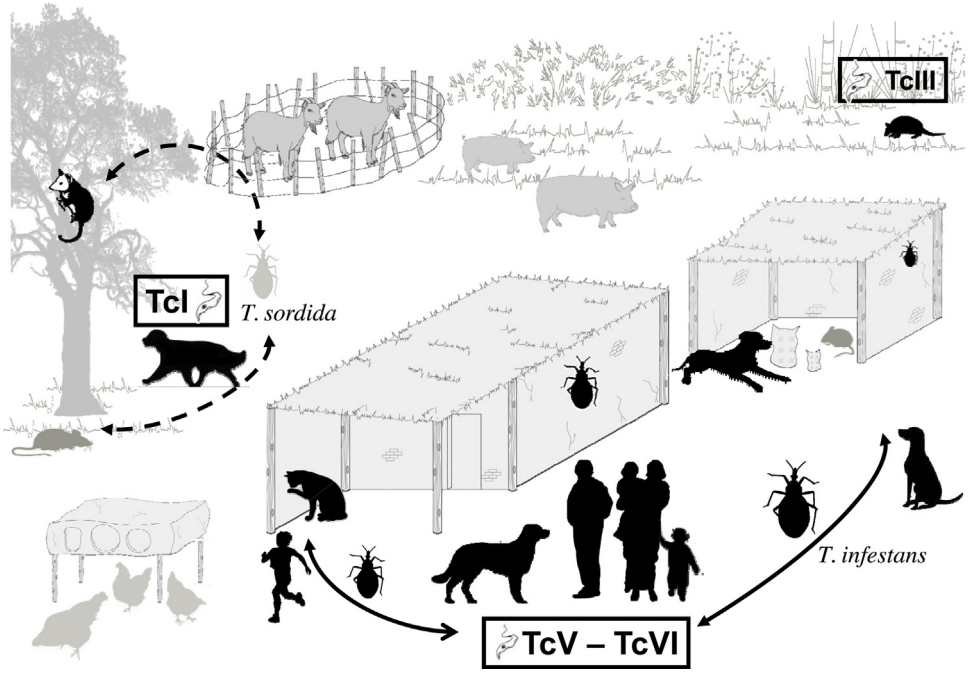

Fig. 3. Current understanding of transmission cycles of T. cruzi in sylvatic and (peri)domestic habitats of Pampa del Indio, in the Argentine Chaco.

human cases had mixed TcV–TcVI infections. We estimated that mixed infections with TcV-TcVI were significantly more frequent than expected from chance alone ($\chi^2 = 4.37$, 1 df, $P < 0.05$). These results indicate a strong linkage between *T. cruzi*, dogs and humans which previous studies using several parasite isolation and genotyping methods failed to reveal; suggest frequent DTU selection by classical methods of parasite isolation, and refute the notion of two independent (peri)domestic transmission cycles occurring in sympatry, in agreement with the other strands of eco-epidemiological evidence reviewed above.

Fig. 3 shows our current understanding of the (peri)domestic transmission cycle of T. cruzi in Pampa del Indio.

4.8. Dogs as sentinel hosts

Domestic dogs have frequently been used as natural sentinels of human exposures to various environmental risks because they display several favorable traits (Anon., 1991): being susceptible to the disease agent and developing a measurable, consistent response to it; share habitats with humans; being accessible, easy to enumerate and capture; and abundant. Unlike domestic cats, dogs comply with these attributes for *T. cruzi* (Sections 4.1–4.7). Domestic dogs may also be used to detect changes in the prevalence and incidence of infection (Halliday et al., 2007), as shown in Fig. 2B (see Section 4.6). On a different note, a trained dog was used to discover hitherto unknown foci of *T. infestans* in sylvatic habitats of the Paraguayan Chaco (Rolón et al., 2011).

The co-occurrence of very low prevalence rates of *T. cruzi* infection in domestic dogs and the absence of domestic bug infestations in areas under surveillance which had been treated with insecticides was taken as evidence that dogs might be used as natural sentinels of Chagas disease vector control status (Forattini et al., 1978; Gamboa, 1967). However, in the absence of information on how dogs had been involved in local domestic transmission cycles before control actions, their use as sentinels is questionable: for example, had dog infections been rare before control interventions, a before–after comparison of infection rates would have shown no impact of a successful intervention against the vector.

The proposed use of dogs as sentinels of the (peri)domestic transmission of *T. cruzi* mediated by *T. infestans* in northwest Argentina was based on the close association between the household presence of infected dogs and infected children or bugs (see Section 4.6; Cardinal et al., 2006; Castañera et al., 1998; Gürtler et al., 1990), and the much greater incidence of infection in dogs (Gürtler et al., 2005, 1987). These relationships appear to be similar elsewhere (Estrada-Franco et al., 2006). For areas in which dogs were substantially infected before control interventions, the occurrence of *T. cruzi* infection in native young dogs born after insecticide spraying campaigns may be used to monitor the interruption of parasite transmission in (peri)domestic habitats, provided in-migration, travel history and other routes of transmission (non-vector or by secondary triatomine species) can be accounted for or are marginal. The probability of congenital transmission of *T. cruzi* in naturally-infected dogs may not be trivial (Cardinal et al., 2006), and reached nearly 10% in experimentally-infected rats (Desquesnes and de Lana, 2010). Domestic dog infection may also be used for risk stratification at district level through comparison of age-infection prevalence curves and derived estimates of force of infection between village clusters (Cardinal et al., 2014).

Domestic dogs may also act as sentinels of sylvatic sources of infection because of their roles as predators or scavengers of infected wild hosts' tissues (Cleaveland et al., 2006). In rural districts from Brazil previously affected by food-borne outbreaks of human Chagas disease linked to putative sylvatic sources, the seroprevalence rates of *T. cruzi* in dogs were high, widely variable among and within ecoregions, and positively associated with the presence of small wild mammals having high parasitemia (Xavier et al., 2012). Whether dog infections and human cases shared the same DTUs apparently remained unknown. In other study sites that experienced repeated oral outbreaks of Chagas disease in Belém (Brazil), the same DTU (TcI) was identified in human cases, dogs and *Rhodnius pictipes* (das Xavier et al., 2014). Domestic dogs and various species of small wild mammals and triatomines also shared TcI in a nature preserve (Rocha et al., 2013), suggesting they were epidemiologically linked.

A thorough interpretation of surveillance data for risk assessment requires consideration of the linkages between animal sentinel events and human health (Rabinowitz et al., 2005). The distribution of *T. cruzi* seropositivity in shelter dogs (8.8%) across Texas (USA) was taken as a spatial index of Chagas disease risk (Tenney et al., 2014). In the virtual absence of established (peri)domestic infestations, dogs most likely became infected with *T. cruzi* from contact with sylvatic triatomines or from eating infected wild hosts. Evidence of both frequent house invasion by infected triatomines during late spring in the same region (Reisenman et al., 2012) and rare autochthonous human cases of *T. cruzi* infection with a putative vector origin (Garcia et al., 2015) suggests seasonal disease threats to dogs. How these threats translate into actual human risk and *T. cruzi* infection depend on the vulnerability of housing to bug invasion, householders' awareness, and their bug control practices. Dog infection on its own may fail to represent adequately human transmission risks in some scenarios.

4.9. Mathematical models of transmission

A mathematical model of the domestic transmission of *T. cruzi* was developed in close connection with the household data collected in Amamá to understand the effects of domestic animals and of alternative control strategies (Cohen and Gürtler, 2001). The model accounted for the effects of humans, dogs, chickens, domestic bugs and seasonality on the prevalence of human and bug infection and other outcome measures. The model predicted that excluding domestic animals from bedrooms, especially infected dogs, would reduce the risk of human and bug infection. Introducing the first few infected dogs in the household increased substantially the abundance of infected bugs in the summer and the human prevalence rate. Increasing the number of chickens in human sleeping quarters (for hypothetical zooprophylactic effects) very slightly decreased the human prevalence rate but increased the size of the infected summer bug population. The available empirical data are consistent with model predictions (Cohen and Gürtler, 2001; Gürtler et al., 2014b, 2005, 1997).

Both the transmission model and data illustrate a paradox: increasing the access to (or introducing) a suitable, non-susceptible host on which bugs blood-feed frequently, such as chickens, increases the infected-bug population in the presence of other domestic reservoir hosts. Chickens therefore are part of the reservoir of infection (Haydon et al., 2002) despite not being susceptible to *T. cruzi*, and increase the household risk of infection rather than exerting zooprophylactic or dilution effects.

Other modeling efforts of the transmission system in northwest Argentina consistently supported the key role dogs play in the domestic eco-epidemiology of *T. cruzi* (Castañera et al., 2003; Coffield et al., 2013; Fabrizio et al., 2014; Spagnuolo et al., 2012). The main qualitative results are robust to the modeling framework, additional transmission routes, whether residual insecticide spraying was conducted, and how frequently.

4.10. Control methods

The menu of control methods for dogs infected with *T. cruzi* includes: permanent vector suppression to block (peri)domestic transmission (Section 4.6); insecticide collars, sprays, pour-ons and ivermectin; and treatment. Euthanasia of *T. cruzi*-infected dogs is neither feasible as a public health measure nor warranted. Pyrethroid-impregnated dog collars suppressed bug populations enclosed in experimental chicken huts and exerted little bug antifeeding effects (Reithinger et al., 2006, 2005). In contrast, fipronil either impregnated in collars or applied as a spray or pour-on formulation on dogs exerted limited effects on the bugs (Gürtler et al., 2009b; Amelotti et al., 2012). Subcutaneous injection of dogs with ivermectin produced increased mortality of *T. infestans* and *R. neglectus* nymphs relative to control dogs until 7 days post-treatment (Dias et al., 2005). Enhanced prevention of dog infections with *T. cruzi* may be achieved through targeted residual insecticide spraying of kennels or other dog resting sites, and use of insecticide-impregnated collars with repellent effects.

Treatment of infected dogs with the two available parasiticidal drugs (benznidazole and nifurtimox) is feasible and moderately effective, more so during the acute phase (Guedes et al., 2002; Haberkorn and Gönnert, 1972). Nifurtimox administered to experimentally-infected beagle dogs at 16–30 mg/kg during 3–4 months suppressed parasitemia, exerted no adverse side effects during treatment, and did not lead to serorecovery in chronic infections followed up over a four-month period (Haberkorn and Gönnert, 1972). Other authors considered that nifurtimox caused more serious adverse reactions (Barr, 2009). Benznidazole suppressed parasitemia during the first year post-treatment, reduced systolic cardiac alterations, but did not prevent the development of dog cardiomyopathy (Santos et al., 2012). Treatment of dogs with these drugs also risks the evolution of drug resistance in *T. cruzi* which could proceed very fast given the high force of infection they are subject to, with potentially severe implications for human treatment.

A live-attenuated vaccine against *T. cruzi* in dogs provided some protection and reduced infectiousness in a field trial (Basombrio et al., 1993). Dogs experimentally infected with *T. cruzi* and vaccinated with *T. rangeli* antigens had reduced parasitemia and infectiousness (Basso et al., 2007). A preventive and therapeutic DNA vaccine reduced parasitemia, cardiac inflammation and cardiac parasite burden in experimentally-infected mongrel dogs (Quijano-Hernández et al., 2013). A combined approach that identifies the most infectious dogs and treats them with an effective therapeutic vaccine suppressing infectiousness is predicted to strongly reduce the risk of infection in vectors and other domestic hosts.

5. Cats and rodents

5.1. Prevalence of infection

Carlos Chagas identified the first mammalian host of *T. cruzi* (a domestic cat) in the same household where the first human infection was later discovered (Chagas, 1909), and apparently considered that both dogs and cats were important domestic reservoir hosts (Deane, 1964). The published data for the occurrence of *T. cruzi* infection in domestic cat populations and in commensal rats and mice (*Rattus* sp. and *Mus musculus*) are historically sparser than for dogs (Tables 2 and 3; Supplementary Tables 2 and 3) (Barretto, 1985; Deane, 1964; Jansen and Roque, 2010; Minter, 1976a; Noireau et al., 2009; WHO, 2002). Extensive cross-sectional surveys documented 18–64% of xenodiagnosis-positive cats in widely separated areas infested by various triatomine species (Table 2). Serological methods were sometimes used to reveal cat infections that were missed by xenodiagnosis (Cardinal et al., 2006; Enriquez et al., 2013).

For commensal rats, the prevalence rates of *T. cruzi* through xenodiagnosis varied very widely up to 100% and covered a wide range of triatomine species and locations (Table 3, Supplementary Table 3). Barretto (1985) compiled several hundreds of xenodiagnostic results from the Rio Grande Medio valley (Brazil) showing an overall infection prevalence of 15.5% for *R. norvegicus* and 25% for *R. rattus*. Mice showed high infection rates (10–30%) in several locations (Table 3, Supplementary Table 3).

Domesticated Andean guinea pigs (*Cavia porcellus*), reared in large numbers for household consumption in Peru and Bolivia, were

Table 2
Infectiousness to the vector of cats naturally infected with *T. cruzi*. This table only includes publications based on at least 10 hosts examined for infection.

Country/locality	Vector species (number nymphs/stage)	Percentage of infectious hosts (no. infectious/no. examined)	Percentage of bugs infected (no. infected/no. examined)	Reference
Argentina, Chaco, Resistencia	*Triatoma infestans* (8 nymphs III or IV)	18.1 (10/55)	NR	Mayer and Alcaraz (1954)
Argentina, Amamá	*T. infestans* (10-20 nymphs III or IV)	NR	61.3 (19/31)	Gürtler et al. (1986b)
Argentina, Trinidad & Mercedes	*T. infestans* (10-20 nymphs III)	39.3 (11/28)	22.2 (171/768)	Gürtler et al. (1993)
Argentina, Chaco, Pampa del Indio	*T. infestans* (10-20 nymphs IV)	50.0 (8/16)[a]	ND	Enriquez et al. (2013)
Argentina, Chaco, Pampa del Indio	*T. infestans* (10-20 nymphs IV)	64.3 (9/14)[a,b]	44.0 (ND)	Enriquez et al. (2014)
Bolivia, Cochabamba	ND	17.6 (3/17)	ND	Román (1947)
Bolivia, Santa Cruz, Porongo	*T. infestans* (7 nymphs III)	7.6 (5/66)	ND	De Muynck et al. (1978)
Brazil, Sao Paulo, Cassia dos Coqueiros	ND	19.7 (97/492)	ND	Freitas (1950)
Brazil, Goiás, Montevidiu	ND	20.0 (2/10)	ND	Freitas and Mendonça (1951)
Brazil, Campo Florido	*T. infestans* (5 nymphs)	25.5 (12/47)	NR	Freitas et al. (1952)
Brazil, Castro Alves	*T. infestans* (10 nymphs V)	18.4 (7/38)	NR	Mott et al. (1978)
Brazil, Ceará Crato, Barbalha	ND	0 (0/107)	ND	Alencar et al. (1963)
Brazil, Bahía	ND	34.8 (8/23)	ND	fide Minter (1976a)
Brazil, São Paulo, Guaíra	ND	0 (0/39)	ND	Forattini et al. (1971)
Brazil, São Paulo, São Joao de Boa Vista	*T. infestans* (10 nymphs IV or V)	0 (0/317)	ND	Forattini et al. (1978)
Brazil, Bahia, Riacho da Santana	*T. infestans* or *R. prolixus* (5 nymphs V)	29.0 (9/31)	ND	Barrett et al. (1979)
Brazil, Minas Gerais, Frutal	NR	0.3 (1/301)	NR	Forattini et al. (1983)
Chile, Huasco, Domeyco	ND	18.1 (4/22)	ND	Gasic and Bertin (1939)
Chile, summary	ND	11.9 (215/1805)	ND	Neghme and Schenone (1963)
Chile, summary 1939–1969	*T. infestans* (7 nymphs III)	11.6 (216/1865)	ND	Schenone (1971)
Chile, Summary 1939–1972	*T. infestans* (7 nymphs III)	11.5 (217/1892)	ND	Schenone et al. (1972)
Chile, Santiago, Colina & Caleu	*T. infestans* (10 nymphs III)	3.7 (1/27)	NR	Rojas et al. (1973)
Costa Rica, San Rafael Ojo de Agua	*T. dimidiata* or *T. infestans* or *R. prolixus* or *R. neglectus* (10 nymphs IV-V)	2.9 (3/102)	NR	Zeledón et al. (1975)

ND, no data; NR, not reported.
[a] Only seropositive animals were examined.
[b] Only animals aged ≥1 year were reported.

frequently infected with *T. cruzi* (range, 0–61%; Table 3, Supplementary Table 3). In Arequipa (Peru), guinea pig enclosures sustained much more abundant populations of *T. infestans* and bug infection rates than domestic premises and chicken coops (Herrer, 1955). The mean infectiousness to bugs of infected guinea pigs that served as control hosts in a vaccine trial was 38% (Basombrío et al., 1987).

5.2. Epidemiological role

The epidemiological role of domestic cats has been a controversial topic (Catalá et al., 2004; Deane, 1964; Gürtler et al., 2007a, 1993; Minter, 1976a; Mott et al., 1978; Piesman et al., 1983; Wisnivesky-Colli et al., 1985). In the past, cats were sometimes considered to play a greater role as sources than dogs because they remained longer indoors and thus were more exposed to triatomines, frequently achieving higher infection rates (Deane, 1964). The debate hinged on the apparent mismatch between the sometimes low frequency of cat blood meals and the high prevalence of cat infection or the household co-occurrence of infectious cats, infected bugs and infected children. Minter (1976a) concluded that "opossums, rodents, and cats thus play no role in bug-mediated *T. cruzi* transmission in houses and the role of the dog is minor" in São Felipe, a *P. megistus*-infested area of Bahia (northeast Brazil), based on the virtual absence of these hosts in a large bloodmeal study. The frequent infections found in local cats and rodents were explained through bug or rodent predation, and a generalized inference was made: "The long-held view that dogs, cats, and other animals are important domestic reservoirs of *T. cruzi* does not hold true when *P. megistus* is the domiciliary vector."

In Castro Alves, another endemic area of Bahia near São Felipe, Mott et al. (1978) found 18% of xenodiagnosis-positive dogs and cats, and a close association between the household seroreactivity for *T. cruzi* in children and the presence of an infected dog or cat. Based on these results and previous xenodiagnostic surveys of humans, dogs and cats (Martins et al., 1945), they concluded: "Domestic dogs and cats were important reservoirs of *T. cruzi* in an endemic area where *P. megistus* is the only domiciliary triatomine vector". All human cases were infected with TcII, and apparently the DTUs infecting dogs and cats remained unknown (Barrett et al., 1980), as did the host-feeding patterns of local triatomines. Subsequent host-feeding studies of *P. megistus* collected from (peri)domestic habitats elsewhere evidenced a large frequency of cat and dog blood meals (Forattini et al., 1981; Steindel et al., 1994).

These case studies illustrate the issues that hamper assessing the relative importance of reservoir hosts on the basis of fragmentary evidence. In addition to heterogeneities in eco-epidemiological context and methods, several sources of bias related to vector sampling (e.g., habitat, season and bug stage), frequent host shifts over a relative long lifespan and the transient presence of highly infectious sources may account for situations in which the host-feeding patterns fail to pinpoint a significant reservoir host. In northwest Argentina, *T. cruzi*-infected cats contributed significantly to domestic bug infection after adjusting for the number of infected dogs in the household (Gürtler et al., 2007a, 1993), and (peri)domestic bugs, dogs and cats shared the same DTUs (Section 4.6).

Rats were important (peri)domestic reservoir hosts of *T. cruzi* in several transmission systems, and also are the hosts of *Trypanosoma conorhini* which is transmitted by *Triatoma rubrofasciata* (Dujardin et al., 2015). Naturally-infected rats had high prevalence of infection and long-lasting parasitemia in Panama (Edgcomb and Johnson, 1970). In Costa Rica, the prevalence of positive xenodiagnosis was 31% in rats and 2% in humans, (peri)domestic *T. dimidiata* fed frequently on *R. rattus*, and 53% of the rat-fed bugs were infected with *T. cruzi* (Zeledón et al., 1975, 1973). Qualitatively similar evidence was collected for domestic *T. barberi* and commensal rodents in Mexico (Zárate et al., 1980).

Table 3
Infectiousness to the vector of commensal rodents naturally infected with *T. cruzi*. This table only includes publications based on at least 10 hosts examined for infection.

Host	Country/ locality	Vector species (number nymphs/stage)	Percentage of infectious hosts (no. infectious/no. examined)	Percentage of bugs infected (no. infected/no. examined)	Reference
Rattus rattus	Venezuela, Caracas valley	*R. prolixus* (III)	2.7 (1/37)	NR	Herrera and Urdaneta-Morales (1997)
Rattus rattus	Bolivia, Cochabambita & Guapomocito	*T. infestans* (7 nymphs III)	38.5 (5/13)	NR	Brenière et al. (1998)
Rattus rattus	Brazil, Ceará	NR (4 triatomines)	0.5 (3/594)	NR	Alencar et al. (1962)
Rattus rattus	Brazil	*T. infestans* (6 nymphs)[a]	12.4 (17/137)	NR	Barretto et al. (1967)
Rattus rattus	Brazil, São Paulo, Salto de Pirapora	NR	0 (0/27)	NR	Forattini et al. (1969)
Rattus rattus	Brazil, Bahía, São Felipe	*R. prolixus* (10 nymphs V)	9.5 (2/21)	NR	Miles (1976)
Rattus rattus	Brazil, São Paulo, São Joao de Boa Vista	*T. infestans* (10 nymphs IV or V)	4.3 (2/47)	NR	Forattini et al. (1978)
Rattus rattus	Brazil, Pará	*R. prolixus* or *P. megistus* (3–10 nymphs III-V)	0 (0/23)	NR	Lainson et al. (1979)
Rattus rattus	Brazil, Bahia, Riacho da Santana	*T. infestans* & *R. prolixus* (5 nymphs V)	100.0 (10/10)	NR	Barrett et al. (1979)
Rattus rattus	Brazil, Minas Gerais, Frutal	NR	2.3 (7/309)	NR	Forattini et al. (1983)
Rattus rattus	Costa Rica, San Rafael Ojo de agua	*T. dimidiata* or *T. infestans* or *R. prolixus* or *R. neglectus* (10 nymphs IV-V)	30.6 (37/121)	NR	Zeledón et al. (1975)
Rattus norvergicus	Brazil, São Paulo, Riberao Preto	*T. infestans, T. sordida* or *P. megistus*	9.1 (1/11)	NR	Barretto et al. (1966)
Rattus norvergicus	Brazil	*T. infestans* (6 nymphs) or 3 + 3 *T. sordida* or 2 from *T. infestans, R. neglectus or P. megistus*)	12.9 (13/101)	NR	Barretto et al. (1967)
Rattus norvergicus	Costa Rica, San Rafael Ojo de agua	*T. dimidiata, T. infestans, R. prolixus*, or *R. neglectus* (10 nymphs IV-V)	3.8 (1/26)	NR	Zeledón et al. (1975)
Rattus sp.	Venezuela, Lara, La Matica and Tintinal	*R. prolixus* (5 nymphs III-IV)	0 (0/68)[b]	NR	Lima et al. (2005)
Rattus sp.	Venezuela, El Carrizal, Merida State	*R. prolixus* (5 nymphs III)	0 (0/15)		Lima et al. (2006)
Mus musculus	Costa Rica, San Rafael Ojo de agua	*T. dimidiata, T. infestans, R. prolixus*, or *R. neglectus* (10 nymphs IV-V)	10.7 (11/103)	NR	Zeledón et al. (1975)
Cavia porcellus	Bolivia, Sacaba Tarata Punata	NR	37.5 (6/16) 31.8 (7/22) 61.1 (11/18)	NR	Torrico (1950)
Cavia sp.	Perú, Moyobamba	*T. infestans, R. prolixus*, or *P. herreri* (8 nymphs II-V)	0 (0/150)	NR	Herrer (1956)
Guinea pigs and rabbits pooled	Chile, summary up to 1948 ND	ND	0 (0/126)	ND	Neghme et al. (1949)

ND, no data; NR, not reported; $ only one nymph was examined.
[a] Alternatively, 3 *T. infestans* and 3 *T. sordida*, or 2 *T. infestans*, 2 *R. neglectus* and 2 *P. megistus* nymphs were used.
[b] 3 rats were positive by hemoculture.

Following an outbreak of human Chagas disease linked to the recent introduction of *T. infestans* into western Bahia, two remarkable studies revealed the key roles of rats and other domestic hosts in Riacho de Santana, some 400 km from Castro Alves and São Felipe (Barrett et al., 1979, 1980). The high proportion of xenodiagnosis-positive dogs (19%), cats (29%) and *R. rattus* (100% of 10 rats), and the co-occurrence of rats and infected bugs in a collection site suggested rats were a significant source of *T. cruzi* for *T. infestans* and *T. sordida*. The authors refrained from using the results of bloodmeal identification tests which were considered unreliable (Barrett et al., 1979). Two different DTUs (TcI and TcII) were present among stocks isolated from humans, dogs, cats and rats, although all *T. infestans* and *T. sordida*, most humans and nearly all rats had TcI (Barrett et al., 1980). These data show strong linkages between different triatomine species, domestic and commensal reservoir hosts, and humans at village level.

The existing evidence at that time therefore supported the prediction that a rodent control program would reduce the risk of domestic bug infection in areas where rodents are important reservoir hosts of *T. cruzi* (Gürtler et al., 1991). Recent data

Table 4
Infectiousness to the vector of goats and pigs naturally infected with *T. cruzi*. This table only includes publications based on at least 10 hosts examined for infection.

Host	Country/ locality	Vector species (number nymphs/stage)	Percentage of infectious hosts (no. infectious/no. examined)	Percentage of bugs infected (no. infected/no. examined)	Reference
Pigs	Venezuela, Anzoátegui	ND	0 (0/11)	ND	Dao (1945)
	Brazil, Bahia	NR	0 (0/200)	ND	fide Minter (1976a)
	Brazil, Pará, Muana	*T. infestans* or *R. prolixus* (5 nymphs V)	2.9 (3/105)	ND	Valente et al. (1998)
	Mexico, Morelos	*Triatoma pallidipennis* (5 nymphs V)	0 (0/20)	ND	Salazar-Schettino et al. (1997)
Goats	Argentina, Córdoba, Cruz del Eje	*T. infestans* (20 nymphs III)	0 (0/34)	NR	Ruiz et al. (1985)
	Chile, summary 1939-1969	*T. infestans* (7 nymphs III)	0.4 (1/233)	ND	Schenone (1971)

NR, not reported; ND, no data.

from Guatemala corroborated that both *M. musculus* and *R. rattus* were frequently infected with *T. cruzi* and served as bloodmeal sources of *T. dimidiata*, and house infestation was closely associated with presence of mice and dogs (Bustamante et al., 2014). A community-operated rodent control trial reduced significantly the house prevalence of *R. rattus* infestation, the relative abundance of mice, and the relative odds of infection with *T. cruzi* in early-stage bugs, as predicted (De Urioste-Stone et al., 2015).

6. Other incidental hosts

6.1. Prevalence of infection

Goats, sheep, pigs, rabbits and equines were exceptionally found infected with *T. cruzi* by parasitological methods (Table 4, Supplementary Table 4) (Barretto, 1987; Desquesnes and de Lana, 2010; Jansen and Roque, 2010; Minter, 1976a; Noireau et al., 2009). Experimental inoculation of young goats, sheep, pigs and calfs proved them susceptible to *T. cruzi* (Diamond and Rubin, 1958). However, young goats inoculated with large doses of *T. cruzi* were infectious during the acute phase, and exceptionally during the chronic phase by hemoculture and xenodiagnosis (Fernandes et al., 1994). Experimental infections of pigs displayed a mild course in which both xenodiagnosis and hemoculture were negative (Marsden et al., 1970). In rabbits, however, the course of experimental infections was highly variable among studies, and parasitemia was detectable by xenodiagnosis during the chronic phase (Desquesnes and de Lana, 2010).

Regarding domestic goats (*Capra hircus*) and sheep (*Ovis aries*), only 1 (0.4%) goat tested xenodiagnosis-positive over three decades of research across Chile (Schenone et al., 1972), whereas subsequent serosurveys reported much higher rates of *T. cruzi*-seropositivity in goats (range, 7.0–17.8%), sheep (2.7–7.0%) and alpacas (*Vicugna pacos*) as determined by an indirect hemagglutination test (IHAT) (Schenone et al., 1991; Table 4, Supplementary Table 4). High seroprevalence rates (26.1%) for *T. cruzi* were also recorded in goats by an indirect immunofluorescence antibody test (IFAT) in Paraíba, northeast Brazil (Fuentes Castillo et al., 1988), whereas a more recent survey recorded <1% of IFAT-positive young goats and sheep in the same region (Bezerra et al., 2014). The interpretation of serological results is not straightforward because domestic ungulates are also infected by other trypanosomes (especially *Trypanosoma evansi* and *Trypanosoma vivax*) and *Phytomonas sp.* that may cause cross-reactions with *T. cruzi* (Herrera et al., 2005; Desquesnes and de Lana, 2010); some of these trypanosomes may also thrive in hemoculture. Cattle (*Bos taurus*) IHAT-positive for *T. cruzi* (35.6%) were attributed to a serological cross-reaction with *Trypanosoma theileri* (Burkholder et al., 1980). More recently, molecular methods revealed very high infection rates in free-ranging domestic goats (36-50%) and the frequent occurrence of domestic DTUs (TcV and TcVI) in goats, wild rodents and *Triatoma spinolai* in a nature preserve in Chile (Botto-Mahan et al., 2005; Rozas et al., 2007). The singularity of these findings relative to earlier ones (Miles et al., 1984) and prevalent patterns elsewhere justifies additional research efforts.

Domestic pigs (*Sus scrofa*) were rarely found parasitologically positive for *T. cruzi* (Pinto, 1942; Salazar-Schettino et al., 1997), whereas seropositivity was more frequent (Supplementary Table 4). The finding of a PCR-positive pig (but no goat, sheep or cattle) was linked to the frequent presence of *T. cruzi*-infected *T. sordida* in Matto Grosso do Sul, Brazil (Cominetti et al., 2011).

Domestic rabbits (*Oryctolagus cuniculus*) tested by xenodiagnosis were rarely found infected with *T. cruzi* (0.9%) in Chile (Schenone et al., 1972), whereas subsequent surveys yielded high seroprevalence rates ranging from 4.1% to 12.1% (Supplementary Table 4). Domestic rabbit infections were also frequent (16%, diagnostics not defined) in Arequipa, southern Peru, where a very small fraction of the houses raised them at times when vector-borne transmission was intense (Naquira et al., 1972).

6.2. Epidemiological role

Despite the fact that goats, sheep and pigs are frequent bloodmeal hosts of Triatominae (Rabinovich et al., 2011), *T. infestans* and other triatomines infesting corrals and pigsties were very rarely infected with *T. cruzi* in the Argentine Chaco (Cardinal et al., 2014; Cecere et al., 1999; Gürtler et al., 2007b). This type of ecotope-stratified bug infection data was sometimes taken as a "natural xenodiagnosis" of the resident hosts. In a province-wide survey of peridomestic foci of *T. infestans* conducted in the southern dry Chaco, detailed searches in a large goat corral with a complex fence structure yielded an estimated total population size of 20,500 bugs, only 3.7% bugs infected with *T. cruzi* (of 2702 insects examined microscopically), and the concurrent presence of rats and mice (Soler et al., 1977).

We identified only one case in which domestic pigs were possibly implicated in a local transmission cycle of *T. cruzi*. In a riverine community of the Brazilian Amazon, three pigs were xenodiagnosis-positive (105 tested), the pigsties adjoining or adjacent to houses were heavily infested with *Panstrongylus geniculatus*, and both pigs and bugs were infected with TcI (Valente et al., 1998). None of 253 human volunteers was positive for *T. cruzi* (by serology or xenodiagnosis) despite their frequent complains of bug bites. *Panstrongylus geniculatus* was also collected from nearby palm trees which harbored xenodiagnosis- positive *Didelphis marsupialis* and another marsupial, both widely known to carry TcI. In the absence of host-feeding and bug infection data for each habitat type, the immediate source(s) of TcI for the infected triatomines cannot be ascertained and pigs implicated beyond doubt. This ground-breaking research illustrates the initial foothold of a sylvatic pathogen and a sylvatic vector in the (peri)domestic interphase within the rainforest. Subsequent surveys in the capital city of Venezuela confirmed the links among *P. geniculatus*, TcI, humans, opossums and rats (Carrasco et al., 2005).

Combined with their very low prevalence of infection and infectiousness, the evidence supports that livestock play a virtually insignificant role as hosts of *T. cruzi*. However, goats, sheep and pigs are non-essential hosts that may contribute indirectly to the reservoir of infection by increasing total bug population size and subsequent invasion of domestic premises, likewise chickens and pigs in the above examples. Qualifying goats, sheep and alpacas as "less important domestic reservoirs" on an equal standing with guinea pigs, rats and mice is clearly misleading (WHO, 2002, p. 56–57). The sparse infection data available for domestic rabbits, the rarity of rabbit blood meals (Rabinovich et al., 2011) and their extreme rarity as a host in traditionally endemic rural areas do not support that "rabbits are important domestic reservoirs of *T. cruzi*" (WHO, 2002, p. 57), although they may have the potential to play that role under particular circumstances.

7. Conclusions

This review highlights that domestic dogs, cats, commensal rodents and domesticated guinea pigs have high reservoir host competence and play key roles as amplifying hosts and sources of *T. cruzi* in many (peri)domestic transmission cycles covering a broad diversity of ecoregions and triatomine species. These hosts are able to maintain *T. cruzi* in the absence of any other host species, and therefore fit into the definition of primary reservoir hosts and maintenance hosts. No other domestic animal plays those roles.

Because of their much higher infectiousness relative to humans and frequent infection with *T. cruzi*, whenever dogs, cats, commensal rodents and domesticated guinea pigs serve as bloodmeal sources they increase the probability of vector and host infection relative to the human-only base case (i.e., increase pathogen abundance) and may also contribute to increased bug population size. In addition to their elevated infectiousness during the acute and early chronic stage of infection (Hoff et al., 1979), a fraction of adult human cases plays a key role as long-term maintenance hosts of *T. cruzi*.

The role of domestic reservoir hosts may vary substantially across space and time because of wide variations in the prevalence of host infection and in vector host-feeding patterns and infection, which are mainly determined by local host diversity and exposures of human and non-human domestic hosts (i.e., ecological factors). These facts and the opportunistic host-feeding behavior of Triatominae advise against sweeping generalizations to the vector species or regional level. Similarly, the utility of an animal sentinel depends both on the ecological context and the aims of the surveillance program. Cultural and socio-economic reasons may jointly explain why in some rural areas householders traditionally allow the entrance of dogs and cats to human sleeping quarters or decide to keep chickens indoors. Rodent infestations vary greatly across settings and seasons, and householders may or may not decide to combat rodents in effective ways or have the means to do so (De Urioste-Stone et al., 2015). Information on local host species composition, abundance and exposures over space and time is greatly needed to advance the understanding of the patterns observed, and so is quantifying the strength of the links among host species and vectors. Integration of eco-epidemiological and genetic-marker data at the appropriate spatiotemporal scales where host-vector interactions occur is essential and has rarely been done.

Unlike widely variable host-vector contact rates, host infectiousness appears to be a host species-level factor which varies within broad limits set by other determinants (e.g., health and nutritional status). Research on host infectiousness is at an early stage, and the development of reliable markers of infectiousness may have broad application for targeted disease prevention. A comprehensive understanding of the epidemiological role of human and non-human hosts will greatly benefit from better, simpler diagnostic tools for host infection and infectiousness, bloodmeal identification, and pathogen genotyping.

Domestic dogs sometimes were a point of entry of sylvatic strains of *T. cruzi* into (peri)domestic habitats (Cardinal et al., 2008; Enriquez et al., 2014; Ramírez et al., 2013; Rocha et al., 2013; Xavier et al., 2012). The propagation of these strains may depend on whether (peri)domestic premises are colonized by triatomines and the putative host-feeding links between dogs and local bugs. The increasing in-migration into previously non-endemic areas, such as the Amazon basin, is creating further opportunities for propagation of sylvatic and domestic parasite strains via humans and dogs, and the occurrence of mixed DTU infections with potential evolutionary implications. Control interventions against commensal rodents are justified on its own, whereas the menu for addressing dog and cat infections is very much limited and culling of asymptomatic animals unjustified. Keeping domestic dogs, cats, commensal rodents and domesticated guinea pigs (including chickens) out of human sleeping quarters and blocking or reducing their exposure to triatomine bugs are predicted to strongly reduce transmission risks.

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Appendix A. Supplementary data

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References

Alencar, J.E., Pessoa, E., Sherlock, V., Sousa, G., Cunha, R., 1962. Estudos sobre a epidemiología de Doenca de Chagas no Ceará. I-Dados Preliminares. Rev. Bras. Malariol. Doenças Trop. 14, 201–219.

Alencar, J.E., Oliveira de Almeida, J., Sherlock, V., Pereira de França, A., Leite, L., 1963. Estudos sçbre a epidemiologia da doenôa de Chagas no Ceará. II Novos dados. Rev Bras. Malariol. Doenças Trop. 15, 551–565.

Alencar, J.E., Almeida, Y.M., Santos, A.R., Freitas, L.M., 1974/1975. Epidemiology of Chagas' disease in the state of Ceará, Brazil. IV. The role of dogs and cats as domestic reservoirs. Rev. Bras. Malariol. Doenças Trop. 26/27, 5–26.

Amelotti, I., Catalá, S.S., Gorla, D.E., 2012. Effects of fipronil on dogs over *Triatoma infestans*, the main vector of *Trypanosoma cruzi*, causative agent of Chagas disease. Parasitol. Res. 111, 1457–1462, http://dx.doi.org/10.1007/s00436-012-2979-6

Anderson, R.M., May, R., 1991. A framework for discussion the population biology of infectious diseases. In: Infectious Diseases of Humans: Dynamics and Control., pp. 13–23.

Andrade, S.G., Campos, R.F., Castro Sobral, K.S., Magalhães, J.B., Pereira Guedes, R.S., Guerreiro, M.L., 2006. Reinfections with strains of *Trypanosoma cruzi*, of different biodemes as a factor of aggravation of myocarditis and myositis in mice. Rev. Soc. Bras. Med Trop. 39, 1–8, http://dx.doi.org/10.1042/BJ20051189

Anon, 1991. Animals as Sentinels of Environmental Hazards. National Academy Press, Washington DC.

Araujo, F.M.G., Bahia, M.T., Magalhães, N.M., Martins-Filho, O.A., Veloso, V.M., Carneiro, C.M., Tafuri, W.L., Lana, M., 2002. Follow-up of experimental chronic Chagas' disease in dogs: use of polymerase chain reaction (PCR) compared with parasitological and serological methods. Acta Trop. 81, 21–31.

Ashford, R.W., 1996. Leishmaniasis reservoirs and their significance in control. Clin. Dermatol. 14, 523–532.

Ashford, R.W., 2000. The leishmaniases as emerging and reemerging zoonoses. Int. J. Parasitol. 30, 1269–1281.

Ashford, R.W., 2003. When is a reservoir not a reservoir. Emerg. Infect. Dis. 9, 1495–1496, http://dx.doi.org/10.3201/eid0911.030088

Barr, S.C., 2009. Canine Chagas' disease (American trypanosomiasis) in North America. Vet. Clin. North Am. Small Anim. Pract. 39, 1055–1064, http://dx.doi.org/10.1016/j.cvsm.2009.06.004, v–vi.

Barrett, T., Hoff, R., Mott, K., Guedes, F., Sherlock, I., 1979. An outbreak of acute Chagas's disease in the São Francisco Valley region of Bahia, Brazil: triatomine vectors and animal reservoirs of *Trypanosoma cruzi*. Trans. R. Soc. Trop. Med. Hyg. 73, 703–709, http://dx.doi.org/10.1016/0035- 9203(79)90025-7

Barrett, T.V., Hoff, R.H., Mott, K.E., Miles, M.A., Godfrey, D.G., Teixeira, R., Almeida de Souza, J.A., Sherlock, I.A., 1980. Epidemiological aspects of three *Trypanosoma cruzi* zymodemes in Bahia State, Brazil. Trans. R. Soc. Trop. Med. Hyg 74, 84–90.

Barretto, M., Siqueira, A.F., Ferrioli, F., Carvalheiro, J.R., 1966. Estudos sobre reservatorios e vectores silvestres do *Trypanosoma cruzi*. XI. Observacoes sobre da tripanossomose americana no Municipio de Ribeirao Preto Saõ Paulo. Rev. Inst. Med. Trop. Sao Paulo 8, 103–112.

Barretto, M., Ferraz de Siqueira, A., Ferriolli Filho, F., Carvalheiro, J.R., 1967. Estudos sôbre reservatórios e vetores silvestres do *Trypanosoma cruzi*. XX: Infecção natural de ratos comensais, capturados em biótopos naturais e artificiais, por tripanossomos semelhantes ao T. cruzi. Rev. Bras. Biol. 27, 145–156.

Barretto, M., 1964. Reservatórios do *Trypanosoma cruzi* nas Américas. Rev. Bras. Malariol. Doenças Trop. 16, 527–552.

Barretto, M.P., 1968. Estudos sôbre reservatórios e vectores silvestres do *Trypanosoma cruzi*. XXXI. Observaçoes sôbre a associação entre reservatórios e

vectores, com especial referência à região nordeste do Estado de São Paulo. Rev. Bras. Biol. 28, 481–494.
Barretto, M., 1985. Reservorios del *Trypanosoma (Schizotrypanum)* cruzi Chagas, 1909. In: Carcavallo, R.U., Rabinovich, J.E., Tonn, R.J. (Eds.), Factores Biológicos Y Ecológicos En La Enfermedad de Chagas. , pp. 275–288.
Basombrío, M.A., Arredes, H., Uncos, D.A., Rossi, R., Alvarez, E., 1987. Field trial of vaccination against American Trypanosomiasis (Chagas'disease) in domestic guinea pigs. Am. J. Trop. Med. Hyg. 37, 57–62.
Basombrio, M.A., Segura, M.A., Mora, M.C., Gomez, L., 1993. Field trial of vaccination against American Trypanosomiasis (Chagas'disease) in dogs. Am. J. Trop. Med. Hyg. 49, 143–151.
Basso, B., Castro, I., Introini, V., Gil, P., Truyens, C., Moretti, E., 2007. Vaccination with *Trypanosoma rangeli* reduces the infectiousness of dogs experimentally infected with *Trypanosoma cruzi*. Vaccine 25, 3855–3858, http://dx.doi.org/10.1016/j.vaccine.2007.01.114
Begon, M., 2008. Effects of host diversity on disease dynamics. In: Ostfeld, R.S., Feesing, F., EV (Eds.), Infectious Disease Ecology. Effects of Ecosystems on Disease and of Disease on Ecosystems. Princeton University Press, pp. 12–29.
Bezerra, C.M., Cavalcanti, de, L.P.G., Souza, de de, R.C.M., Barbosa, S.E., Xavier, das, S.C.C., Jansen, A.M., Ramalho, R.D., Diotaiut, L., 2014. Domestic, peridomestic and wild hosts in the transmission of *Trypanosoma cruzi* in the Caatinga area colonised by *Triatoma brasiliensis*. Mem. Inst. Oswaldo Cruz 109, 887–898.
Botto-Mahan, C., Ortiz, S., Rozas, M., Cattan, P.E., Solari, A., 2005. DNA evidence of *Trypanosoma cruzi* in the Chilean wild vector *Mepraia spinolai* (Hemiptera: Reduviidae). Mem. Inst. Oswaldo Cruz 100, 237–239, http://dx.doi.org/10.1590/S0074-02762005000300003
Brenière, S.F., Bosseno, M.F., Telleria, J., Bastrenta, B., Yacsik, N., Noireau, F., Alcazar, J.L., Barnabé, C., Wincker, P., Tibayrenc, M., 1998. Different behavior of two *Trypanosoma cruzi* major clones: transmission and circulation in young Bolivian patients. Exp. Parasitol. 89, 285–295, http://dx.doi.org/10.1006/expr.1998.4295
Brunner, J.L., LoGiudice, K., Ostfeld, R.S., 2008. Estimating reservoir competence of *Borrelia burgdorferi* hosts: prevalence and infectivity, sensitivity, and specificity. J. Med. Entomol. 45, 139–147, http://dx.doi.org/10.1093/jmedent/45.1.139
Burkholder, J.E., Allison, T.C., Kelly, V.P., 1980. *Trypanosoma cruzi* (Chagas) (Protozoa: Kinetoplastida) in invertebrate, reservoir, and human hosts of the lower Rio Grande Valley of Texas. J. Parasitol. 66, 305–311.
Bustamante, J.M., Novarese, M., Rivarola, H.W., Lo Presti, M.S., Fernández, A.R., Enders, J.E., Fretes, R., Paglini-Oliva, P.A., 2007. Reinfections and *Trypanosoma cruzi* strains can determine the prognosis of the chronic chagasic cardiopathy in mice. Parasitol. Res. 100, 1407–1410, http://dx.doi.org/10.1007/s00436-006-0425-3
Bustamante, D., De Urioste-Stone, S., Juarez, J., Pennington, P., 2014. Ecological, social and biological risk factors for continued *Trypanosoma cruzi* transmission by *Triatoma dimidiata* in Guatemala. PLoS One 9, e104599, http://dx.doi.org/10.1371/journal.pone.0104599
Canese, A., 1978. Datos actualizados sobre conocimientos epidemiológicos de la enfermedad de Chagas en el Paraguay. Rev. Parag. Microbiol. 13, 7–20.
Cardinal, M., Castañera, M., Lauricella, M., Cecere, M., Ceballos, L., Vazquez-Prokopec, G., Kitron, U., Gürtler, R., 2006. A prospective study of the effects of sustained vector surveillance following community-wide insecticide application on *Trypanosoma cruzi* infection of dogs and cats in rural northwestern Argentina. Am J. Trop. Med. Hyg. 75, 753–761.
Cardinal, M.V., Lauricella, M.A., Marcet, P.L., Orozco, M.M., Kitron, U., Gürtler, R.E., 2007. Impact of community-based vector control on house infestation and *Trypanosoma cruzi* infection in *Triatoma infestans*, dogs and cats in the Argentine Chaco. Acta Trop. 103, 201–211, http://dx.doi.org/10.1016/j.actatropica.2007.06.007
Cardinal, M.V., Lauricella, M.A., Ceballos, L.A., Lanati, L., Marcet, P.L., Levin, M.J., Kitron, U., Gürtler, R.E., Schijman, A.G., 2008. Molecular epidemiology of domestic and sylvatic *Trypanosoma cruzi* infection in rural northwestern Argentina. Int. J. Parasitol. 38, 1533–1543, http://dx.doi.org/10.1016/j.ijpara.2008.04.010
Cardinal, M.V., Orozco, M.M., Enriquez, G.F., Ceballos, L.A., Gaspe, M.S., Alvarado-Otegui, J.A., Gurevitz, J.M., Kitron, U., Gürtler, R.E., 2014. Heterogeneities in the ecoepidemiology of *Trypanosoma cruzi* infection in rural communities of the Argentinean Chaco. Am. J. Trop. Med. Hyg. 90, 1063–1073, http://dx.doi.org/10.4269/ajtmh.13-0251
Carrasco, H.J., Torrellas, A., García, C., Segovia, M., Feliciangeli, M.D., 2005. Risk of *Trypanosoma cruzi* I (Kinetoplastida: Trypanosomae) transmission by *Panstrongylus* (Hemiptera: Reduviidae) in Caracas (Metropolitan District) and neighboring States, Venezuela. Int. J. Parasitol. 35, 1379–1384.
Castañera, M.B., Lauricella, M.A., Chuit, R., Gürtler, R.E., 1998. Evaluation of dogs as sentinels of the transmission of *Trypanosoma cruzi* in a rural area of north-western Argentina. Ann. Trop. Med. Parasitol. 92, 671–683.
Castañera, M.B., Aparicio, J.P., Gürtler, R.E., 2003. A stage-structured stochastic model of the population dynamics of *Triatoma infestans*, the main vector of Chagas disease. Ecol. Model 162, 33–53, http://dx.doi.org/10.1016/S0304-3800(02)388-5
Castañera, M.B., 1999. Contribución de los perros a la transmisión de *Trypanosoma cruzi* en un área rural de Argentina: demografía, rol centinela y modelado matemático. University of Buenos, Aires, PhD Thesis.
Catalá, S.S., Crocco, L.B., Muñoz, A., Morales, G., Paulone, I., Giraldez, E., Candioti, C., Ripol, C., 2004. Entomological aspects of Chagas disease transmission in the domestic habitat, Argentina. Rev. Saúde Públ 38, 216–222.
Catalá, S., 1991. The biting rate of *Triatoma infestans* in Argentina. Med. Vet. Entomol. 5, 325–333.
Ceballos, L.A., Cardinal, M.V., Vazquez Prokopec, G.M., Lauricella, M.A., Orozco, M.M., Cortinas, R., Schijman, A.C., Levin, M.J., Kitron, U., Gürtler, R.E., 2006. Long- term reduction of *Trypanosoma cruzi* infection in sylvatic mammals following deforestation and sustained vector surveillance in northwestern Argentina. Acta Trop. 98, 286–296.
Cecere, M.C., Castañera, M.B., Canale, D.M., Chuit, R., Gürtler, R.E., 1999. *Trypanosoma cruzi* infection in Triatoma infestans and other triatomines: long-term effects of a control program in rural northwestern Argentina. Rev. Panam. Salud Publica 5, 392–399, http://dx.doi.org/10.1007/s11130-009-0132-1
Cedillos, R.A., Warren, M., Wilton, D.P., Jeffery, G.M., Sauerbrey, M., 1976. Estudios epidemiológicos del *Trypanosoma cruzi* en El Salvador. Rev. Inst. Inv. Med. 5, 119–131.
Cerisola, J.A., Rohwedder, R., Segura, E., del Prado, C., Alvarez, M., de Martini, G., 1974. *El xenodiagnóstico*. Instituto de Diagnóstico e Investigación de la Enfermedad de Chagas Dr. Mario Fatala Chabén, Secretaría del Estado de Salud Pública, Ministerio de Bienestar Social, Argentina. Buenos Aires, Argentina.
Chagas, C., 1909. Nova tripanozomiaze humana. Estudos sobre a morfolojia e o ciclo evolutivo do *Schizotrypanum cruzi* n. gen., n. sp., ajente etiolojico de nova entidade morbida do homem. Mem. Inst. Oswaldo Cruz 1, 159–219.
Chapman, M.D., Baggaley, R.C., Godfrey-Fausset, P.F., Malpas, T.J., White, G., Canese, J., Miles, M.A., 1984. *Trypanosoma cruzi* from the Paraguayan Chaco: Isoenzime profiles of strains isolated at Makthlawaiya. J. Protozool. 31, 482–486.
Chaves, L.F., Hernandez, M.-J., Dobson, A.P., Pascual, M., 2007. Sources and sinks: revisiting the criteria for identifying reservoirs for American cutaneous leishmaniasis. Trends Parasitol. 23, 311–316, http://dx.doi.org/10.1016/j.pt.2007.05.003
Clark, H., Dunn, H., 1932. Experimental studies on Chagas' disease in Panama. Am. J. Trop. Med 12, 49–77.
Cleaveland, S., Meslin, F.X., Breiman, R., 2006. Dogs can play useful role as sentinel hosts for disease. Nature 440, 605, http://dx.doi.org/10.1038/440605b
Coffield, D.J., Spagnuolo, A.M., Shillor, M., Mema, E., Pell, B., Pruzinsky, A., Zetye, A., 2013. A model for Chagas disease with oral and congenital transmission. PLoS One 8, e67267, http://dx.doi.org/10.1371/journal.pone.0067267
Cohen, J.E., Gürtler, R.E., 2001. Modeling household transmission of American trypanosomiasis. Science 293, 694–698.
Cominetti, M.C., Andreotti, R., Oshiro, E.T., Dorval, M.E.M.C., 2011. Epidemiological factors related to the transmission risk of *Trypanosoma cruzi* in a Quilombola community, State of Mato Grosso do Sul, Brazil. Rev. Soc. Bras. Med. Trop. 44, 576–581.
Cornejo, A., Cubas, E., Eyzaguirra, G., Dominguez, P., Bitrich, H., Gómez, R., Cornejo, J., 1963. Chagas' disease in southern Peru. Epidemiologic, clinical, electrocardiographic and prophylactic study. An. Fac. Med. Lima 46, 587–609.
Coura, J.R., Dias, J.C.P., 2009. Epidemiology, control and surveillance of Chagas disease: 100 years after its discovery. Mem. Inst. Oswaldo Cruz 104, 31–40, http://dx.doi.org/10.1590/S0074-02762009000900006
Crisante, G., Rojas, A., Teixeira, M.M.G., Añez, N., 2006. Infected dogs as a risk factor in the transmission of human *Trypanosoma cruzi* infection in western Venezuela. Acta Trop. 98, 247–254, http://dx.doi.org/10.1016/j.actatropica.2006.05.006
Cruz-Chan, J.V., Bolio-González, M., Colín-Flores, R., Ramirez-Sierra, M.J., Quijano-Hernandez, I., Dumonteil, E., 2009. Immunopathology of natural infection with *Trypanosoma cruzi* in dogs. Vet. Parasitol. 162, 151–155, http://dx.doi.org/10.1016/j.vetpar.2009.02.024
Dao, L., 1945. La enfermedad de Chagas en el Distrito Aragua (Est. Anzoátegui, Venezuela). Rev. Policlínica Caracas 14, 398–442.
De Leo, G.A., Dobson, A.P., 1996. Allometry and simple epidemic models for microparasites. Nature 379, 720–722, http://dx.doi.org/10.1038/379720a0
De Muynck, A., Garron, A., Bermúdez, H., Zuna, H., Romero, A., Romero, F., García, A., Prado, J., Queirolo, L., Ribera, B., 1978. Estudio epidemiológico de la Enfermedad de Chagas en Porongo, Departamento de Santa Cruz, Bolivia. Bol. Inf. CENETROP 6, 88–97.
De Urioste-Stone, S.M., Pennington, P.M., Pellecer, E., Aguilar, T.M., Samayoa, G., Perdomo, H.D., Enríquez, H., Juárez, J.G., 2015. Development of a community-based intervention for the control of Chagas disease based on peridomestic animal management: an eco-bio-social perspective. Trans. R. Soc. Trop. Med. Hyg. 109, 159–167, http://dx.doi.org/10.1093/trstmh/tru202
Deane, L., 1964. Animal reservoirs of *Trypanosoma cruzi* in Brazil. Rev. Bras. Malariol. Doenças Trop. 16, 27–48.
Desquesnes, M., de Lana, M., 2010. Veterinary aspects and experimental studies. In: Telleria, J., Tibayrenc, M. (Eds.), American Trypanosomiasis Chagas Disease One Hundred Years of Research. Elsevier Inc, pp. 277–318.
Diamond, L.S., Rubin, R., 1958. Experimental infection of certain farm mammals with a North American strain of *Trypanosoma cruzi* from the raccoon. Exp. Parasitol. 7, 383–390.
Dias, J.C., 2000. Carlos Chagas Filho e a doença de Chagas. Alguns tracos a luz de confidencias e inconfidencias. Rev. Soc. Bras. Med. Trop. 33, 325–329.
Dias, J.C.P., Schofield, C.J., Machado, E.M., Fernandes, A.J., 2005. Ticks, ivermectin, and experimental Chagas disease. Mem. Inst. Oswaldo Cruz 100, 829–832, /S0074-02762005000800002.
Diosque, P., Barnabé, C., Padilla, A.M., Marco, J.D., Cardozo, R.M., Cimino, R.O., Nasser, J.R., Tibayrene, M., Basombrío, M.A., 2003. Multilocus enzyme electrophoresis analysis of *Trypanosoma cruzi* isolates from a geographically

restricted endemic area for Chagas Disease in Argentina. Int. J. Parasitol 33, 997–1003.
Diosque, P., Padilla, A.M., Cimino, R.O., Cardozo, R.M., Sanchez Negrette, O., Marco, J.D., Zaca, R., Meza, C., Juarez, A., Rojo, H., Rey, R., Corrales, R.M., Nasser, J.R., Basombrío, M.A., 2004. Chagas disease in rural areas of Chaco province, Argentina: epidemiologic survey in humans, reservoirs, and vectors. Am. J. Trop. Med. Hyg. 71, 590–593.
Dobson, A., 2004. Population dynamics of pathogens with multiple host species. Am. Nat. 164, S64–S78, http://dx.doi.org/10.1086/424681, Suppl.
Dujardin, J.P., Lam, T.X., Khoa, P.T., Schofield, C.J., **2015**. The rising importance of *Triatoma rubrofasciata*. Mem. Inst. Oswaldo Cruz 110, 319–323, http://dx.doi.org/10.1590/0074-02760140446
Dumonteil, E., Nouvellet, P., Rosecrans, K., Ramirez-Sierra, M.J., Gamboa-León, R., Cruz-Chan, V., Rosado-Vallado, M., Gourbière, S., 2013. Eco- Bio-Social determinants for house infestation by non-domiciliated *Triatoma dimidiata* in the Yucatan Peninsula, Mexico. PLoS Negl. Trop Dis. 7, 1–9, http://dx.doi.org/10.1371/journal.pntd.0002466
Dye, C., 1992. The analysis of parasite transmission by blood sucking insects. Ann. Rev. Entomol. 37, 1–19.
Edgcomb, J.H., Johnson, C.M., 1970. Natural infection of *Rattus rattus* by *Trypanosoma cruzi* in Panamá. Am. J. Trop. Med. Hyg. 19, 767–769.
Eloy, L.J., Lucheis, S.B., 2012. Hemoculture and Polymerase Chain Reaction using primers TCZ1/TCZ2 for the diagnosis of canine and feline trypanosomiasis. Vet. Sci. 2012, 419378, http://dx.doi.org/10.5402/2012/419378
Enriquez, G.F., Cardinal, M.V., Orozco, M.M., Schijman, A.G., Gürtler, R.E., 2013. Detection of *Trypanosoma cruzi* infection in naturally infected dogs and cats using serological, parasitological and molecular methods. Acta Trop. 126, 211–217, http://dx.doi.org/10.1016/j.actatropica.2013.03.001
Enriquez, G.F., Bua, J., Orozco, M.M., Wirth, S., Schijman a, G., Gürtler, R.E., Cardinal, M.V., 2014. High levels of *Trypanosoma cruzi* DNA determined by qPCR and infectiousness to *Triatoma infestans* support dogs and cats are major sources of parasites for domestic transmission. Infect. Genet. Evol. 25, 36–43, http://dx.doi.org/10.1016/j.meegid.2014.04.002
Estrada-Franco, J.G., Bhatia, V., Diaz-Albiter, H., Ochoa-García, L., Barbabosa, A., Vazquez-Chagoyan, J.C., Martinez-Perez, M.A., Guzman-Bracho, C., Grag, N., 2006. Human *Trypanosoma cruzi* infection and seropositivity in dogs, Mexico. Emerg. Infect. Dis. 12, 624–630.
Fabrizio, M., Schweigmann, N., Bartoloni, N., 2014. Modelling American trypanosomiasis in an endemic zone: application to the initial spread of household infection in the Argentine Chaco. Zoonoses Public Heal 61, 545–559.
Fenton, A., Pedersen, A.B., 2005. Community epidemiology framework for classifying disease threats. Emerg. Infect. Dis. 11, 1815–1821.
Fernández, M.D.P., Cecere, M.C., Lanati, L.A., Lauricella, M.A., Schijman, A.G., Gürtler, R.E., Cardinal, M.V., 2014. Geographic variation of *Trypanosoma cruzi* discrete typing units from *Triatoma infestans* at different spatial scales. Acta Trop. 140, 10–18, http://dx.doi.org/10.1016/j.actatropica.2014.07.014
Fernandes, A.J., Vitor, R.W., Dias, J.C., 1994. Parasitologic and serological evaluation of caprines experimentally inoculated with *Trypanosoma cruzi*. Rev. Inst. Med. Trop. Sao Paulo 36, 11–17.
Forattini, O.P., Juarez, E., Rabello, E.X., Pattoli, D., Corrêa, R.R., 1969. Infestação domiciliar por *Triatoma infestans* e alguns aspectos epidemiológicos da Tripanossomose Americana em área do Estado de São Paulo, Brasil. Rev. Saude Publ. 3, 159–172.
Forattini, O.P., Ferreira, O.A., da Rocha e Silva, E.O., Rabello, E.X., Santos, J., 1971. Aspectos Ecológicos da Tripanossomose Americana. II. Distribuição e dispersão local de triatomíneos em ecótopos naturais e artificiais. Rev. Saude Publ. 5, 163–191.
Forattini, O.P., Rocha e Silva, E.O., da, Rabello, E.X., Andrade, J.C.R., de, Rodrigues, V.L.C.C., 1978. Aspectos ecológicos da tripanossomíase americana. XIII. – Potencial enzoótico doméstico em área de ocorrência de *Panstrongylus megistus*, sob vigilância epidemiológica. Rev. Saude Publ. 12, 417–424.
Forattini, O.P., Soares Barata, J.M., Ferreira Santos, J.L., Silveira, A.C., 1981. Hábitos alimentares, infecção natural e distribuição de triatomíneos domiciliados na região nordeste do Brasil. Rev. Saude Publ 15, 113–164.
Forattini, O.P., Ferreira, O.A., Rabello, E.X., Barata, J.M., Santos, J.L., 1983. Ecological aspects of South American trypanosomiasis. XVII. Development of Triatominae regional domiciliation in an endemic center of *Triatoma sordida*. Rev. Saude Publ 17, 159–199.
Freitas, J.L.P., Mendonça, W., 1951. Inquerito sôbre moléstia de Chagas no município do Rio Verde. Hosp. Rio Janeiro 39, 251–261.
Freitas, J.L.P., Rocha, U.F., Zapatel Vasquez, J.A., Aftimus, T.N., 1952. Inquérito preliminar sôbre a infecção pelo *Trypanosoma cruzi* (Chagas, entre cães e gatos domésticos no Município de Campo Florido (Triángulo Mineiro), Minas erais, Brasil. Rev. Fac. Med. Vet. Sao Paulo 4, 545–551.
Freitas, J.L.P., 1950. Observacoes sôbre xenodiagnósticos practicados em reservatórios domésticos e silvestres do *Trypanosoma cruzi* em uma localidade endémica da moléstia de Chagas no estado de Sao Paulo. Hosp. Rio Janeiro 38, 63–71.
Fuentes Castillo, A., Marzochi, M.C.A., Modena, C.M., Silva, V.L., Bandéira, D., Judah, A., 1988. Epidemiological survey of human and caprine infection by *Trypanosoma cruzi* in a rural area of the state of Paraiba. Mem. Inst. Oswaldo Cruz 83 (Suppl 1), 196.
Fung, H.L., Calzada, J., Saldaña, A., Santamaria, A.M., Pineda, V., Gonzalez, K., Chaves, L.F., Garner, B., Gottdenker, N., 2014. Domestic dog health worsens with socio-economic deprivation of their home communities. Acta Trop. 135, 67–74, http://dx.doi.org/10.1016/j.actatropica.2014.03.010
Funk, S., Nishiura, H., Heesterbeek, H., Edmunds, W.J., Checchi, F., 2013. Identifying transmission cycles at the human-animal interface: the role of animal reservoirs in maintaining gambiense human african trypanosomiasis. PLoS Comput. Biol. 9, e1002855, http://dx.doi.org/10.1371/journal.pcbi.1002855
Gürtler, R.E., Lauricella, M., Solarz, N.D., Bujas, M.A., Wisnivesky-Colli, C., 1986a. Dynamics of transmission of *Trypanosoma cruzi* in a rural area of Argentina. I–The dog reservoir: an epidemiological profile. Rev. Inst. Med. Trop. Sao Paulo 28, 28–35.
Gürtler, R.E., Solard, N.D., Lauricella, M.A., Haedo, A.S., Pietrokovski, S.M., Alberti, A.A., Wisnivesky-Colli, C., 1986b. Dynamics of transmission of *Trypanosoma cruzi* in a rural area of Argentina. III. Persistence of *T. cruzi* parasitemia among canine reservoirs in a two year follow-up. Rev. Inst. Med. Trop. 28, 213–219.
Gürtler, R.E., Wisnivesky-Colli, C., Solarz, N.D., Lauricella, M., Bujas, M.A., 1987. Dynamics of transmission of *Trypanosoma cruzi* in a rural area of Argentina: II. Household infection patterns among children and dogs relative to the density of infected *Triatoma infestans*. Bull. Pan Am. Health Organ. 21, 280–292.
Gürtler, R.E., Kravetz, F.O., Petersen, R.M., Lauricella, M.A., Wisnivesky-Colli, C., 1990. The prevalence of *Trypanosoma cruzi* and the demography of dog populations after insecticidal spraying of houses: a predictive model. Ann. Trop. Med. Parasitol. 84, 313–323.
Gürtler, R.E., Cecere, M.C., Rubel, D.N., Petersen, R.M., Schweigmann, N.J., Lauricella, M.A., Bujas a, M., Segura, E.L., Wisnivsky-Colli, C., 1991. Chagas disease in north-west Argentina: Infected dogs as a risk factor for the domestic transmission of *Trypanosoma cruzi*. Trans. R. Soc. Trop. Med Hyg. 85, 741–745, http://dx.doi.org/10.1016/0035-9203(91)90440-A
Gürtler, R.E., Cecere, M.C., Rubel, D.N., Schweigmann, N.J., 1992a. Determinants of the domiciliary density of *Triatoma infestans*, vector of Chagas'disease. Med. Vet. Entomol. 6, 75–83.
Gürtler, R.E., Petersen, R.M., Lauricella, M.A., Wisnivesky-Colli, C., 1992b. Infectivity to the vector *Triatoma infestans* of dogs infected with *Trypanosoma cruzi* in north-west Argentina. Ann. Trop. Med. Parasitol. 86, 111–119.
Gürtler, R.E., Cécere, M.C., Petersen, R.M., Rubel, D.N., Schweigmann, N.J., 1993. Chagas disease in north-west Argentina: association between *Trypanosoma cruzi* parasitaemia in dogs and cats and infection rates in domestic *Triatoma infestans*. Trans. R. Soc. Trop. Med. Hyg. 87, 12–15.
Gürtler, R.E., Cecere, M.C., Castañera, M.B., Canale, D., Lauricella, M.A., Chuit, R., Cohen, J.E., Segura, E.L., 1996a. Probability of infection with *Trypanosoma cruzi* of the vector *Triatoma infestans* fed on infected humans ans dogs in northwest Argentina. Am. J. Trop. Med. Hyg. 55, 24–31.
Gürtler, R.E., Cecere, M.C., Vazquez, D.F., Chuit, R., Cohen, J.E., 1996b. Host-feeding patterns of domiciliary *Triatoma infestans* (Hemiptera: Reduviidae) in northwest Argentina: seasonal and instar variation. J. Med. Entomol. 33, 15–26.
Gürtler, R.E., Cohen, J.E., Cecere, M.C., Chuit, R., 1997. Shifting host choices of the vector of Chagas disease, *Triatoma infestans*, in relation to the availability of hosts in houses in northwest Argentina. J. Appl. Ecol. 34, 699–715.
Gürtler, R.E., Chuit, R., Cecere, M.C., Castañera, M.B., Cohen, J.E., Segura, E.L., 1998a. Household prevalence of seropositivity for *Trypanosoma cruzi* in three rural villages in northewestern Argentina: environmental demographic, and entomologic associations. Am. J. Trop. Med. Hyg. 59, 741–749.
Gürtler, R.E., Cohen, J.E., Cecere, M.C., Lauricella, M.A., Chuit, R., Segura, E.L., 1998b. Influence of humans and domestic animals on the household prevalence of *Trypanosoma cruzi* in *Triatoma infestans* populations in northwest Argentina. Am. J. Trop. Med. Hyg. 58, 748–758.
Gürtler, R.E., Cecere, M.C., Lauricella, M.A., Petersen, R.M., Chuit, R., Segura, E.L., Cohen, J.E., 2005. Incidence of *Trypanosoma cruzi* infection among children following domestic reinfestation after insecticide spraying in rural northwestern Argentina. Am. J. Trop. Med. Hyg. 73, 95–103.
Gürtler, R., Cecere, M., Lauricella, M., Cardinal, M., Kitron, U., Cohen, J., 2007a. Domestic dogs and cats as sources of *Trypanosoma cruzi* infection in rural northwestern Argentina. Parasitology 134, 69–82, http://dx.doi.org/10.1017/S003118001259
Gürtler, R., Kitron, U., Cecere, M., Segura, E., Cohen, J., 2007b. Sustainable vector control and management of Chagas disease in the Gran Chaco, Argentina. Proc. Natl. Acad. Sci. U. S. A. 104, 16194–16199, http://dx.doi.org/10.1073/pnas.0700863104
Gürtler, R.E., Ceballos, L.A., Ordóñez-Krasnowski, P., Lanati, L.A., Stariolo, R., Kitron, U., 2009a. Strong host-feeding preferences of the vector *Triatoma infestans* modified by vector density: implications for the epidemiology of Chagas disease. PLoS Negl. Trop. Dis. 3, e447, http://dx.doi.org/10.1371/journal.pntd.0000447
Gürtler, R.E., Ceballos, L.A., Stariolo, R., Kitron, U., Reithinger, R., 2009b. Effects of topical application of fipronil spot-on on dogs against the Chagas disease vector *Triatoma infestans*. Trans. R. Soc. Trop. Med. Hyg. 103, 298–304, http://dx.doi.org/10.1016/j.trstmh.2008.09.018
Gürtler, R.E., Cecere, M.C., Fernández, M.D.P., Vazquez- Prokopec, G.M., Ceballos, L.A., Gurevitz, J.M., Kitron, U., Cohen, J.E., 2014a. Key source habitats and potential dispersal of *Triatoma infestans* populations in northwestern Argentina: implications for vector control. PLoS Negl. Trop. Dis. 8, e3238, http://dx.doi.org/10.1371/journal.pntd.0003238
Gürtler, R.E., Cecere, M.C., Vázquez-Prokopec, G.M., Ceballos, L.A., Gurevitz, J.M., Fernández, M.D.P., Kitron, U., Cohen, J.E., 2014b. Domestic animal hosts strongly influence human-feeding rates of the Chagas disease vector *Triatoma infestans* in Argentina. PLoS Negl. Trop Dis. 8, e2894, http://dx.doi.org/10.1371/journal.pntd.0002894

Gage, K.L., Kosoy, M.Y., 2005. Natural history of plague: perspectives from more than a century of research. Annu. Rev Entomol. 50, 505–528, http://dx.doi.org/10.1146/annurev.ento.50.071803.130337
Gamboa, J.C., 1967. Evaluación de las medidad antitriatomas por medio de la prevalencia de *Schizotrypanum cruzi* en perros. Bol. Inf. Dir. Malariol. San. Amb. 7, 321–325.
Garcia, M.N., Aguilar, D., Gorchakov, R., Rossmann, S.N., Montgomery, S.P., Rivera, H., Woc-Colburn, L., Hotez, P.J., Murray, K.O., 2015. Evidence of autochthonous Chagas disease in southeastern Texas. Am. J. Trop. Med Hyg. 92, 325–330, http://dx.doi.org/10.4269/ajtmh14-0238
Gasic, G., Bertin, V., 1939. Animales reservorios de virus de la Tripanosomosis Americana en Chile (vol. prel.). Rev. Inst. Med. Trop. Sao Paulo 2, 247–261.
Gasic, G., 1943. Algunos hechos sobre clínica y epidemiología de la enfermedad de Chagas en Chile. Bol. Ofic. Sanit. Panam 22, 327–335.
Giojalas, L.C., Catala, S.S., Asin, S.N., Gorla, D.E., 1990. Seasonal changes in infectivity of domestic populations of *Triatoma infestans*. Trans. R. Soc. Trop. Med. Hyg. 84, 439–442, http://dx.doi.org/10.1016/0035-9203(90)90355-I
Guedes, P.M.D.M., Veloso, V.M., Tafuri, W.L., Galvão, L.M.D.C., Carneiro, C.M., Lana, M., Chiari, E., Ataide Soares, K., Bahia, M.T., 2002. The dog as model for chemotherapy of the Chagas' disease. Acta Trop. 84, 9–17, http://dx.doi.org/10.1016/S0001-706X(02)139-0
Gurevitz, J.M., Ceballos, L.A., Gaspe, M.S., Alvarado-Otegui, J.A., Enríquez, G.F., Kitron, U., Gürtler, R.E., 2011. Factors affecting infestation by *Triatoma infestans* in a rural area of the humid Chaco in Argentina: a multi-model inference approach. PLoS Negl. Trop. Dis. 5, e1349, http://dx.doi.org/10.1371/journal.pntd.0001349
Gutierrez, Y., 1962. Tripanosomiasis humana en Colombia. Caldas Med. 3, 65–78.
Haberkorn, A., Gönnert, R., 1972. Animal experimental investigation into the activity of nifurtimox against *Trypanosoma cruzi*. Arzneim. Forsch. (Drur Res.) 22, 1570–1582.
Halliday, J.E.B., Meredith, A.L., Knobel, D.L., Shaw, D.J., Bronsvoort de, B.M.C., Cleaveland, S., 2007. A framework for evaluating animals as sentinels for infectious disease surveillance. J. R. Soc. Interface 4, 973–984, http://dx.doi.org/10.1098/rsif.2007.0237
Hartemink, N.A., Randolph, S.E., Davis, S.A., Heesterbeek, J.A.P., 2008. The basic reproduction number for complex disease systems: defining R(0) for tick-borne infections. Am. Nat. 171, 743–754, http://dx.doi.org/10.1086/587530
Haydon, D.T., Cleaveland, S., Taylor, L.H., Laurenson, M.K., 2002. Identifying reservoirs of infection: a conceptual and practical challenge. Emerg. Infect. Dis. 8, 1468–1473, http://dx.doi.org/10.3201/eid0812.010317
Herrer, A., 1955. Trypanosomiasis americana en el Perú: III. Importancia del cobayo como reservorio de la enfermedad de Chagas en la región sudoccidental. Rev. Med. Exp. Lima 9, 45–55.
Herrer, A., 1956. Observaciones sobre la enfermedad de Chagas en la Provincia de Moyobamba (Departamento de San Martín). Rev. Med. Exp. Lima 10, 59–74.
Herrera, L., Urdaneta-Morales, S., 1997. Synanthropic rodent reservoirs of *Trypanosoma* (*Schizotrypanum*) *cruzi* in the valley of Caracas, Venezuela. Rev. Inst. Med. Trop. Sao Paulo 39, 279–282, http://dx.doi.org/10.1590/S0036-46651997000500006
Hoare, C., The trypanosomes of mammals. A zoological monograph. 1972. Oxford: Blackwell.
Hoff, R., Mott, K.E., França Silva, J., Menezes, V., Hoff, J.N., Barrett, T.V., Sherlock, I., 1979. Prevalence of parasitemia and seroreactivity to *Trypanosoma cruzi* in a rural population of northeast Brazil. Am. J. Trop. Med. Hyg. 28, 461–466.
Jansen, A.M., Roque, A.L.R., 2010. Domestic and Wild Mammalian Reservoirs. In: Telleria, J., Tibayrenc, M. (Eds.), American Trypanosomiasis Chagas Disease One Hundred Years of Research. Elsevier Inc., 249-276, http://dx.doi.org/10.1016/B978-0-12-384876-5.00011-3
Kjos, S., Snowden, K., Craig, T., Lewis, B., Ronald, N., Olson, J., 2008. Distribution and characterization of canine Chagas disease in Texas. Vet. Parasitol. 152, 249–256.
Kribs-Zaleta, C., 2010. Estimating contact process saturation in sylvatic transmission of *Trypanosoma cruzi* in the United States. PLoS Negl. Trop. Dis 4, e656, http://dx.doi.org/10.1371/journal.pntd.0000656
Lainson, R., Shaw, J.J., Fraiha, H., Miles, M.A., Draper, C.C., 1979. Chagas'disease in the Amazon basin: I. *Trypanosoma cruzi* infections in silvatic mammals, triatomine bugs and man in the State of Para, north Brazil. Trans. R. Soc. Trop. Med. Hyg. 73, 193–204.
Lauricella, M.A., Riarte, A., Lazzari, J.O., Barousse, A.P., Segura, E.L., 1986. Enfermedad de Chagas en perros experimentalmente infectados con *Trypanosoma cruzi*. Medicina (B. Aires) 46, 195–2000.
Lauricella, M.A., Sinagra, A.J., Paulone, I., Riarte, A.R., Segura, E.L., 1989. Natural *Trypanosoma cruzi* infection in dogs of endemic areas of the Argentine Republic. Rev. Inst. Med. Trop. Sao Paulo 31, 63–70.
Lauricella, M.A., Castañera, M.B., Gürtler, R., Segura, E.L., 1998. Immunodiagnosis of *Trypanosoma cruzi* (Chagas' disease) infection in naturally infected dogs. Mem. Inst. Oswaldo Cruz 93, 501–507.
Lima, H., De Rodríguez, A., Flores, F., Galindo, W., Convit, J., 2005. Molecular identification of Trypanosoma cruzi in Didelphis marsupialis and Rattus spp. in an old endemic area of Chagas disease in Lara State Venezuela. Bol. Malariol. Salud Amb. 45, 101–109.
Lima, H., Carrero, J., Rodríguez, A., de Guglielmo, Z., Rodríguez, N., 2006. Trypanosomatidae of public health importance occurring in wild and synanthropic animals of rural Venezuela. Biomedica 26, 42–50.
Lucheis, S.B., Da Silva, A.V., Meira, D.A., Marcondes-Machado, J., 2005. Trypanosomatids in dogs belonging to individuals with chronic Chagas' disease living in Botucatu town and surrounding region, São Paulo State, Brazil. J. Venom. Toxins. Incl. Trop. Dis. 11, 492–509.
Luz, Z.M.P., Coutinho, M.G., Cançado, J.R., Krettli, A.U., 1994. Hemoculture: sensitive technique in the detection of *Trypanosoma cruzi* in chagasic patients in the chronic phase of Chagas disease. Rev. Soc. Bras. Med. Trop. 7, 143–148.
Macchiaverna, N., Gaspe, M.S., Enriquez, G.F., Tomassone, L., Gürtler, R.E., Cardinal, M.V., 2015. *Trypanosoma cruzi* infection in *Triatoma sordida* before and after community-wide residual insecticide spraying in the Argentinean Chaco. Acta Trop. 143, 97–102.
Machado, E.M.M., Fernandes, A.J., Murta, S.M.F., Vitor, R.W.A., Júnior, D.J.C., Pinheiro, S.W., Lopes, E.R., Adad, S.J., Romanha, A.J., Dias, J.C., 2001. A study of experimental reinfection by *Trypanosoma cruzi* in dogs. Am. J. Trop. Med. Hyg. 65, 959–965.
Maffey, L., Cardinal, M., V, Ordóñez-Krasnowski, P.C., Lanati, L.A., Lauricella, M.A., Schijman, A.G., Gürtler, R.E., 2012. Direct molecular identification of *Trypanosoma cruzi* discrete typing units in domestic and peridomestic *Triatoma infestans* and *Triatoma sordida* from the Argentine Chaco. Parasitology 139, 1570–1579, http://dx.doi.org/10.1017/S0031182012000856
Marcili, A., Lima, L., Cavazzana, M., Junqueira, A.C.V., Veludo, H.H., Maia Da Silva, F., Campaner, M., Paiva, F., Nunes, V.L.B., Teixeira, M.M.G., 2009a. A new genotype of *Trypanosoma cruzi* associated with bats evidenced by phylogenetic analyses using SSU rDNA, cytochrome b and Histone H2B genes and genotyping based on ITS1 rDNA. Parasitology 136, 641–655, http://dx.doi.org/10.1017/S0031182009005861
Marcili, A., Lima, L., Valente, V.C., Valente, S.A., Batista, J.S., Junqueira, A.C.V., Souza, A.I., da Rosa, J.A., Campaner, M., Lewis, M.D., Llewellyn, M.S., Miles, M.A., Teixeira, M.M.G., 2009b. Comparative phylogeography of *Trypanosoma cruzi* TCIIc: new hosts, association with terrestrial ecotopes, and spatial clustering. Infect. Genet. Evol. 9, 1265–1274, http://dx.doi.org/10.1016/j.meegid.2009.07.003
Marsden, P.D., Hagstrom, J.W.C., 1968. Experimental *Trypanosoma cruzi* infection in beagle puppies. The effect of variations in dose and source of infecting trypanosomes and the route of inoculation on the course of the infection. Trans. R. Soc. Trop. Med Hyg. 62, 816–824.
Marsden, P.D., Blackie, E.J., Rosenberg, M.E., Ridley, D.S., Hagstrom, J.W., 1970. Experimental *Trypanosoma cruzi* infections in domestic pigs (*Sus scrofa domestica*). Trans. R. Soc. Trop. Med. Hyg. 64, 156–158.
Martins, A., Versiani, W., Tupinambá, A., 1945. Estudos sobre a molástia de Chagas no Estado de Minas Gerais. I. Estudo epidemiológico de um foco de moléstia no Municipio de Jaboticatubas. Arq. Inst. Quim. Biol. 1, 51–61.
Mather, T.N., Wilson, M.L., Moore, S.I., Ribeiro, J.M.C., Spielman, A., 1989. Comparing the relative potential of rodents as reservoirs of the Lyme disease spirochete (*Borrelia burgdorferi*). Am. J. Epidemiol. 130, 143–150.
Matter, H., Daniels, T., 2000. Dog ecology and population biology. In: Macpherson, C., Meslin, F., Wandeler, A. (Eds.), Dogs, Zoonoses and Public Health. CABI, New York, pp. 17–50.
Mayer, H.F., Alcaraz, I., 1954. Investigaciones sobre Esquizotripanosis en perros y gatos de la zona suburbana de Resistencia. An. Inst. Med. Reg. 4, 9–17.
Mazza, S., Jörg, M.E., 1936. Infecciön natural mortal por *S. cruzi* en cachorro de perro Pila de Jujuy. 9na Reun. Soc. Arg. Patol. Reg. N. 1, 365–411.
Mazza, S., Lobos, M.M., 1937. Casos de enfermedad de Chagas y animales domésticos infectados naturalmente con *S. cruzi* comprobados en el Departamento de Trancas provincia de Tucumán. MEPRA 32, 18–33.
Mazza, S., 1934. Difusión de la infección natural por Schyzotripanum cruzi en perros de la Provincia de Jujuy. MEPRA 17, 23–28.
Mazza, S., 1936. Comprobaciones de casos agudos de Enfermedad de Chagas en nuevas partes de la zona biológica chaqueña (Formosa, Chaco Salteño) Hallazgos epidemiológicos especiales de la región. MEPRA 27, 3–47.
Miles, M.A., Apt, B.W., Widmer, G., Povoa, M.M., Schofield, C.J., 1984. Isozyme heterogeneity and numerical taxonomy of *Trypanosoma cruzi* stocks from Chile. Trans. R. Soc. Trop. Med. Hyg. 78, 526–535.
Miles, M.A., Llewellyn, M.S., Lewis, M.D., Yeo, M., Baleela, R., Fitzpatrick, S., Gaunt, M.W., Mauricio, I.L., 2009. The molecular epidemiology and phylogeography of *Trypanosoma cruzi* and parallel research on *Leishmania*: looking back and to the future. Parasitology 136, 1509–1528, http://dx.doi.org/10.1017/S0031182009990977
Miles, M.A., Distribution and importance of Triatominae as Vector of *Trypanosoma cruzi*, in: New Approaches in American Trypanosomiasis Research, 1976. Pan American Health Organization. Scientific Publications No. 318., pp. 48–56.
Minter, D.M., 1976a. Effects on transmission to man of the presence of domestic animals in infested households. In: New Approaches in American Trypanosomiasis Research. Pan American Health Organization, Washington DC, pp. 330–337, No 318.
Minter, D.M., 1976b. Feeding patterns of some triatomine vector species. In: New Approaches in American Trypanosomiasis Research. Pan American Health Organization, pp. 33–47, No. 318.
Monje-Rumi, M.M., Brandán, C.P., Ragone, P.G., Tomasini, N., Lauthier, J.J., Alberti D'Amato, A.M., Cimino, R.O., Orellana, V., Basombrío, M., Diosque, P., 2015. *Trypanosoma cruzi* diversity in the Gran Chaco: Mixed infections and differential host distribution of TcV and TcVI. Infect. Genet. Evol. 29, 53–59, http://dx.doi.org/10.1016/j.meegid.2014.11.001
Montenegro, V.M., Jiménez, M., Dias, J.C., Zeledón, R., 2002. Chagas disease in dogs from endemic areas of Costa Rica. Mem. Inst. Oswaldo Cruz 97, 491–494.

Mott, K.E., Mota, E.A., Sherlock, I., Hoff, R., Muniz, T.M., Oliveira, T.S., Draper, C.C., 1978. *Trypanosoma cruzi* infection in dogs and cats and household seroreactivity to *T. cruzi* in a rural community in northeast Brazil. Am. J. Trop. Med. Hyg. 27, 1123–1127.
Naquira, F., Córdoba, E., Neira, M., Valdivi, L., 1972. Epidemiología de la Enfermedad de Chagas en el Perú, in: Simposio Internacional Sobre Enfermedad de Chagas, 26 de Noviembre Al 2 de Diciembre. Sociedad Argentina de Parasitología. Buenos Aires. pp. 201–207.
Neghme, A., Schenone, H., 1963. Enfermedad de Chagas en Chile: veinte años de investigación. An. Cong. Int. Doenca Chagas (Rio de Janeiro, 1959), 3., pp. 1069–1105.
Neghme, R., Román, J., Sotomayor, R., 1949. Nuevos datos sobre la enfermedad de Chagas en Chile. Bol. Ofic. Sanit. Panam 28, 808–817.
Noireau, F., Diosque, P., Jansen, A.M., 2009. *Trypanosoma cruzi*: adaptation to its vectors and its hosts. Vet. Res. 40, http://dx.doi.org/10.1051/vetres/2009009
Nouvellet, P., Dumonteil, E., Gourbière, S., 2013. The improbable transmission of *Trypanosoma cruzi* to human: the missing link in the dynamics and control of Chagas disease. PLoS Negl. Trop. Dis. 7, e2505, http://dx.doi.org/10.1371/journal.pntd.0002505
Orozco, M., Ceballos, L., Pino, M., Gürtler, R., 2013a. Local threats and potential infectious hazards to maned wolves (*Chrysocyon brachyurus*) in the southeastern Argentine Chaco. Mammalia 78, 339–349, http://dx.doi.org/10.1515/mammalia-2013-0067
Orozco, M.M., Enriquez, G.F., Alvarado-Otegui, J.A., Cardinal, M.V., Schijman, A.G., Kitron, U., Gürtler, R.E., 2013b. New sylvatic hosts of *Trypanosoma cruzi* and their reservoir competence in the humid Chaco of Argentina: a longitudinal study. Am. J. Trop. Med. Hyg. 88, 872–882, http://dx.doi.org/10.4269/ajtmh.12-0519
Perez, C., Stagno, S., Welch, E., Villarroel, F., 1970. Infeccion chagásica humana y animal en viviendas rociadas previamente con insecticidas. Bol. Chile Parasitol 25, 33–36.
Petersen, R.M., Gürtler, R.E., Cecere, M.C., Rubel, D.N., Lauricella, M.A., Hansen, D., Carlomagno, M.A., 2001. Association between nutritional indicators and infectivity of dogs seroreactive for *Trypanosoma cruzi* in a rural area of northwestern Argentina. Parasitol. Res. 87, 208–214.
Piesman, J., Sherlock, I.A., Christensen, H.A., 1983. Host availability limits population density of *Pastrongylus megistus*. Am. J. Trop. Med. Hyg. 32, 1445–1450.
Pifano, C.F., 1973. La dinámica epidemiológica de la enfermedad de Chagas en el Valle de los Naranjos, Estado Carabobo, Venezuela. II. La infección chagásica en la población rural del area. Arch. Venez. Med. Trop. Parasitol. Med. 5, 31–45.
Pineda, V., Saldaña, A., Monfante, I., Santamaría, A., Gottdenker, N.L., Yabsley, M.J., Rapoport, G., Calzada, J.E., 2011. Prevalence of trypanosome infections in dogs from Chagas disease endemic regions in Panama, Central America. Vet. Parasitol. 178, 360–363, http://dx.doi.org/10.1016/j.vetpar.2010.12.043
Pinto, C., 1942. Tripanosomiasis cruzi (Doença de Carlos Chagas) no Rio Grande do Sul, Brasil. Mem. Inst. Oswaldo Cruz 37, 443–537.
Pizarro, J.C., Stevens, L., 2008. A new method for forensic DNA analysis of the blood meal in Chagas disease vectors demonstrated using *Triatoma infestans* from Chuquisaca, Bolivia. PLoS One 3, e3585, http://dx.doi.org/10.1371/journal.pone.0003585
Quijano-Hernández, I.A., Castro-Barcena, A., Vázquez-Chagoyán, J.C., Bolio-González, M.E., Ortega-López, J., Dumonteil, E., 2013. Preventive and therapeutic DNA vaccination partially protect dogs against an infectious challenge with *Trypanosoma cruzi*. Vaccine 31, 2246–2252, http://dx.doi.org/10.1016/j.vaccine.2013.03.005
Quinnell, R.J., Courtenay, O., 2009. Transmission, reservoir hosts and control of zoonotic visceral leishmaniasis. Parasitology 136, 1915–1934, http://dx.doi.org/10.1017/S0031182009991156
Rabinovich, J., Solarz, N.D., Gurtler, R., Wisnivesky-Colli, C., 1990. Probability of transmission of Chagas disease by *Triatoma infestans* (Hemiptera: Reduviidae) in an endemic area of Santiago del Estero, Argentina. Bull. World Heal. Organ 68, 737–746.
Rabinovich, J.E., Kitron, U.D., Obed, Y., Yoshioka, M., Gottdenker, N., Chaves, L.F., 2011. Ecological patterns of blood-feeding by kissing-bugs (Hemiptera: Reduviidae: Triatominae). Mem. Inst. Oswaldo Cruz 106, 479–494.
Rabinowitz, P.M., Gordon, Z., Holmes, R., Taylor, B., Wilcox, M., Chudnov, D., Nadkarni, P., Dein, F.J., 2005. Animals as sentinels of human environmental health hazards: an evidence – based analysis. Ecohealth 2, 26–37.
Ramírez, J.D., Turriago, B., Tapia-Calle, G., Guhl, F., 2013. Understanding the role of dogs (*Canis lupus familiaris*) in the transmission dynamics of *Trypanosoma cruzi* genotypes in Colombia. Vet. Parasitol. 196, 216–219, http://dx.doi.org/10.1016/j.vetpar.2012.12.054
Reisenman, C.E., Savary, W., Cowles, J., Gregory, T.L., Hildebrand, J.G., 2012. The distribution and abundance of triatomine insects, potential vectors of Chagas Disease, in a metropolitan area in southern Arizona, United States. J. Med. Entomol. 49, 1254–1261.
Reithinger, R., Davies, C.R., 1999. Is the domestic dog (*Canis familiaris*) a reservoir host of American cutaneous leishmaniasis? A critical review of the current evidence. Am. J. Trop. Med. Hyg 61, 530–541.
Reithinger, R., Ceballos, L., Stariolo, R., Davies, C.R., Gürtler, R.E., 2005. Chagas disease control: deltamethrin-treated collars reduce *Triatoma infestans* feeding success on dogs. Trans. R. Soc. Trop. Med. Hyg. 99, 502–508.
Reithinger, R., Ceballos, L., Stariolo, R., Davies, C.R., Gürtler, R.E., 2006. Extinction of experimental *Triatoma infestans* populations following continuous exposure to dogs wearing deltamethrin-treated collars. Am. J. Trop. Med. Hyg. 74, 766–771.
Riarte, A., Sinagra, A., Lauricella, M., Bolomo, N., Moreno, M., Cossio, P., Arana, R., Segura, E.L., 1995. Chronic experimental infection by *Trypanosoma cruzi* in *Cebus apella* monkeys. Mem. Inst. Oswaldo Cruz 90, 733–740.
de Rocha, U.F., de Siqueira, A.F., 1958. Inquérito sóbre a prevaléncia do *Trypanosoma cruzi* em animais domésticos em localidade desinsetizada. Cienc. Cult. 10, 141.
Rocha, F.L., Roque, A.L.R., Arrais, R.C., Santos, J.P., Lima, V.D.S., Xavier, S.C.D.C., Cordeir-Estrela, P., D'Andrea, P.S., Jansen, A.M., 2013. *Trypanosoma cruzi* TcI and TcII transmission among wild carnivores, small mammals and dogs in a conservation unit and surrounding areas, Brazil. Parasitology 140, 160–170, http://dx.doi.org/10.1017/S0031182012001539
Roellig, D.M., Brown, E.L., Barnabé, C., Tibayrenc, M., Steurer, F.J., Yabsley, M.J., 2008. Molecular typing of *Trypanosoma cruzi* isolates, United States. Emerg. Infect. Dis. 14, 1123–1125, http://dx.doi.org/10.3201/eid1407.080175
Rogers, D.J., 1988. The dynamics of vector-transmitted diseases in human communities. Phil. Trans. R. Soc. L. 321, 513–539.
Rojas, A., Sotelo, J.M., Villaroel, F., Contreras Mdel, C., 1973. La importancia del perro y el gato en la epidemiología de la enfermedad de Chagas. Bol. Chile Parasitol. 28, 42–43.
Rolón, M., Vega, M.C., Román, F., Gómez, A., de Arias, A.R., 2011. First report of colonies of sylvatic *Triatoma infestans* (Hemiptera: Reduviidae) in the Paraguayan Chaco, using a trained dog. PLoS Negl. Trop. Dis. 5, e1026, http://dx.doi.org/10.1371/journal.pntd.0001026
Román, P.J., 1947. Contribución al estudio de la epidemiología de la enfermedad de Chagas en Bolivia. Rev. Chile Hig. Med. Prev. 9, 61–81.
Roque, A.L.R., Xavier, S.C.C., Da Rocha, M.G., Duarte, A.C.M., D'Andrea, P.S., Jansen, A.M., 2008. *Trypanosoma cruzi* transmission cycle among wild and domestic mammals in three areas of orally transmitted Chagas disease outbreaks. Am. J. Trop. Med. Hyg. 79, 742–749.
Rozas, M., Botto-Mahan, C., Coronado, X., Ortiz, S., Cattan, P.E., Solari, A., 2007. Coexistence of *Trypanosoma cruzi* genotypes in wild and periodomestic mammals in Chile. Am. J. Trop. Med. Hyg. 77, 647–653.
Ruiz, A., Wisnivesky-Colli, C., Gürtler, R., 1985. Infección por *Trypanosoma cruzi* en humanos, perros y cabras en áreas rurales de la provincia de Córdoba. Medicina (B. Aires) 45, 539–546.
Salazar-Schettino, P.M., Bucio, M.I., Cabrera, M., Bautista, J., 1997. First case of natural infection in pigs. Review of *Trypanosoma cruzi* reservoirs in Mexico. Mem. Inst. Oswaldo Cruz 92, 499–502.
Santos, F.M., Lima, W.G., Gravel, A.S., Martins, T.A.F., Talvani, A., Torres, R.M., Bahia, M.T., 2012. Cardiomyopathy prognosis after benznidazole treatment in chronic canine Chagas' disease. J. Antimicrob. Chemother. 67, 1987–1995, http://dx.doi.org/10.1093/jac/dks135
Schenone, H., Rojas, A., Villarroel, F., Knierim, F., 1972, Epidemiología de la Enfermedad de Chagas en Chile, Simposio Internacional Sobre Enfermedad de Chagas, 26 de Noviembre Al 2 de Diciembre. Sociedad Argentina de Parasitología. Buenos Aires. pp. 189–193.
Schenone, H., Villarroel, F., Alfaro, E., 1978. Epidemiologia de la enfermedad de Chagas en Chile: condiciones de la viviendas relacionadas con la presencia de *Triatoma infestans* y la proporción de humanos y animales infectados con *Trypanosoma cruzi*. Bol. Chile Parasitol. 33, 2–7.
Schenone, H., Contreras, M.C., Borgoño, J.M., Maturana, R., Salínas, P., Sandoval, L., Rojas, A., Tello, P., Villarroel, F., 1991. Overview of the epidemiology of Chagas' disease in Chile. Bol. Chile Parasitol. 46, 19–30.
Schenone, H., 1971. Status of epidemiological research in Chile on Chagas disease. Bol. Ofic. Sanit. Panam. 70, 250–255.
Siqueira, A.F., Magalhães, A.E.A., Rêgo, S.F.M., 1957. Inquérito preliminar sôbre a moléstia de Chagas em uma fazenda do Município de Ribeirão Prêto. Rev. Bras. Malariol. Doenças Trop. 9, 271–276.
Soler, C., Knez, N., Neffen, L., 1977. Importancia del estudio de los factores socio-económicos en la enfermedad de Chagas-Mazza. La Rioja. Focos peridomésticos. Serv. Nac. Chagas-Mazza; La Rioja 17.
Spagnuolo, A.M., Shillor, M., Kingsland, L., Thatcher, A., Toeniskoetter, M., Wood, B., 2012. A logistic delay differential equation model for Chagas disease with interrupted spraying schedules. J. Biol. Dyn. 6, 377–394, http://dx.doi.org/10.1080/17513758.2011.587896
Steindel, M., Toma, H.K., de Carvalho Pinto, C.J., Grisard, E.C., Schlemper Jr., B.R., 1994. Colonization of artificial ecotopes by *Panstrongylus megistus* in Santa Catarina Island, Florianópolis, Santa Catarina, Brazil. Rev. Inst. Med. Trop. Sao Paulo 36, 43–50.
Tenney, T.D., Curtis-Robles, R., Snowden, K.F., Hamer, S.A., 2014. Shelter dogs as sentinels for *Trypanosoma cruzi* transmission across Texas. Emerg. Infect. Dis. 20, 1323–1326, http://dx.doi.org/10.3201/eid2008.131843
Tonn, R.L., de Hubsch, R., Sukerman, E., Torrealba, J.W., Carrasquero, B., 1978. Estudio epidemiológico sobre la enfermedad de Chagas en ocho centros poblados del estado Cojedes, Venezuela. Bol. Dir. Malariol. San. Amb. 18, 3–15.
Torrico, R., 1950. Conocimientos actuales sobre la epidemiología de la enfermedad de Chagas en Bolivia. Bol. Ofic. Sanit. Panam 29, 827–840.
Valente, V.C., Valente, S.A., Noireau, F., Carrasco, H.J., Miles, M.A., 1998. Chagas disease in the Amazon Basin: association of *Panstrongylus geniculatus* (Hemiptera: Reduviidae) with domestic pigs. J. Med. Entomol. 35, 99–103.
Vallejo, G.A., Guhl, F., Schaub, G.A., 2009. Triatominae- *Trypanosoma cruzi*/*T. rangeli*: Vector-parasite interactions. Acta Trop. 110, 137–147, http://dx.doi.org/10.1016/j.actatropica.2008.10.001
Viana, M., Mancy, R., Biek, R., Cleaveland, S., Cross, P.C., Lloyd-Smith, J.O., Haydon, D.T., 2014. Assembling evidence for identifying reservoirs of infection. Trends Ecol. Evol. 29, 270–279, http://dx.doi.org/10.1016/j.tree.2014.03.002

WHO, 2002. *Control of Chagas Disease*. WHO Tech Rep Series 905, Geneva, Switzerland.
WHO, 2015. Chagas disease in Latin America: an epidemiological update based on 2010 estimates. Wkly. Epidemiol. Rec. 90, 33–44.
Whiting, C., 1946. Contribución al estudio de las reservas de parásitos de la enfermedad de Chagas en Chile. Primeros hallazgos en Chile de mamíferos silvestres infestados infestados por *Trypanosoma cruzi*. Rev. Chil. Hyg. Med. Prev. 8, 69–102.
Williams, G.D., Adams, L.G., Yaeger, R.G., McGrath, R.K., Read, W.K., Bilderback, W.R., 1977. Naturally occurring Trypanosomiasis (Chagas disease) in dogs. JAVMA 171, 171–177.
Wisnivesky-Colli, C., Gürtler, R.E., Solarz, N.D., Lauricella, M.A., Segura, E.L., 1985. Epidemiological role of humans, dogs and cats in the transmission of *Trypanosoma cruzi* in a central area of Argentina. Rev. Inst. Med. Trop. Sao Paulo 27, 346–352.
Xavier, S.C., Das, C., Roque, A.L.R., dos Lima, V.S., Monteiro, K.J.L., Otaviano, J.C.R., da Silva, L.F.C.F., Jansen, A.M., 2012. Lower richness of small wild mammal species and Chagas disease risk. PLoS Negl. Trop. Dis. 6, e1647, http://dx.doi.org/10.1371/journal.pntd.0001647
das Xavier, S.C.C., Roque, A.L.R., Bilac, D., de Araújo, V.A.L., da Neto, S.F.C., Lorosa, E.S., da Silva, L.F.C.F., Jansen, A.M., 2014. Distantiae transmission of *Trypanosoma cruzi*: a new epidemiological feature of acute Chagas disease in Brazil. PLoS Negl. Trop. Dis 8, e2878, http://dx.doi.org/10.1371/journal.pntd.0002878
Zárate, L.G., Zárate, Tempelis, R.J., Goldsmith, C.H., RS, 1980. The biology and behavior of *Triatoma barberi* (Hemiptera: Reduviidae) in Mexico. I. Blood meal sources and infection with *Trypanosoma cruzi*. J. Med. Entomol. 17, 103–116.
Zeledón, R., Solano, G., Zúñiga, A., Swartzwelder, J.C., 1973. Biology and ethology of *Triatoma dimidiata* (Latreille, 1811) III. Habitat and blood sources. J. Med. Entomol. 10, 363–370.
Zeledón, R., Solano, G., Burstin, L., Swartzwelder, J.C., 1975. Epidemiological pattern of Chagas disease in an endemic area of Costa Rica. Am. J. Trop. Med. Hyg. 24, 214–225.
Zeledón, R., Dias, J.C.P., Brilla- Salazar, A., Marcondes de Rezende, J., Vargas, L.G., Urbina, A., 1988. Does a spontaneous cure for Chagas disease exist? Rev. Soc. Bras. Med. Trop. 21, 15–20.
Zeledón, R., 1974. Epidemiology, modes of transmission and reservoir hosts of Chagas' Disease, in: Trypanosomiasis and Leishmaniasiswith Special Reference to Chagas' Disease. Ciba Foundation Symposium 20 (New Series), Amsterdam, pp. 51–85.
Zeledon, R., Solano, G., Burstin, L., Swartzwelder, J.C., 1975. Epidemiological pattern of Chagas' disease in an endemic area of Costa Rica. Am. J. Trop. Med. Hyg. 24, 214–225.
Zingales, B., Miles, a, M., Campbell, a, D., Tibayrenc, M., Macedo, A.M., Teixeira, M.M.G., Schijman, A.G., Llewellyn, M.S., Lages-Silva, E., Machado, C.R., Andrade, S.G., Sturm, N.R., 2012. The revised *Trypanosoma cruzi* subspecific nomenclature: Rationale, epidemiological relevance and research applications. Infect. Genet. Evol. 12, 240–253, http://dx.doi.org/10.1016/j.meegid.2011.12.009.