

Eco-Epidemiology of Vector-Borne Transmission of *Trypanosoma cruzi* in Domestic Habitats



Ricardo E. Gürtler, María del Pilar Fernández, and Marta Victoria Cardinal

Abstract Triatomine species largely differ in their degrees of adaptation to thrive in domestic habitats, blood-feed on humans, and transmit *Trypanosoma cruzi*. Pathogen transmission dynamics are shaped by ecological, biological, and social factors. Here we link housing quality and host availability to the host-feeding patterns of domestic triatomines and examine how their blood-feeding performance affects temperature-dependent vital rates and bug population dynamics. The stability/instability habitat divide connects with the large/small triatomine population size dichotomy and on whether bug population dynamics are density-dependent or density-independent and dominated by stochasticity. Seasonal variations in temperature acting on triatomine blood-feeding activity and human-vector contact rates determined the spring peak of symptomatic acute cases of Chagas disease in northern Argentina across four decades. The presence of domestic animals (dogs, cats, and chickens) and commensal rodents increases domestic infestation, vector infection, and parasite transmission across multiple settings and triatomine species. Both ecological and social factors contribute to human infection risk through social vulnerability, mobility patterns, and housing instability. Understanding the interactions among eco-bio-social factors may lead to the design and implementation of improved, sustainable disease control or elimination strategies.

R. E. Gürtler (✉) · M. V. Cardinal

Laboratorio de Eco-Epidemiología, Facultad de Ciencias Exactas y Naturales, Universidad de Buenos Aires, Ciudad Universitaria, Buenos Aires, Argentina

Instituto de Ecología, Genética y Evolución de Buenos Aires, Consejo Nacional de Investigaciones Científicas y Técnicas, Ciudad Universitaria, Buenos Aires, Argentina

e-mail: gurtler@ege.fcen.uba.ar; mvcardinal@ege.fcen.uba.ar

M. del Pilar Fernández

Laboratorio de Eco-Epidemiología, Facultad de Ciencias Exactas y Naturales, Universidad de Buenos Aires, Ciudad Universitaria, Buenos Aires, Argentina

Instituto de Ecología, Genética y Evolución de Buenos Aires, Consejo Nacional de Investigaciones Científicas y Técnicas, Ciudad Universitaria, Buenos Aires, Argentina

Earth Institute, Columbia University, New York, NY, USA

e-mail: mpf2131@columbia.edu

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A. Guarneri, M. Lorenzo (eds.), *Triatominae - The Biology of Chagas Disease Vectors*, Entomology in Focus 5, https://doi.org/10.1007/978-3-030-64548-9_17

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Keywords Habitat suitability · Vector host-feeding patterns · Population dynamics · Parasite transmission · Reservoir hosts · Socio-ecological systems

1 Background

The transmission of zoonotic and vector-borne diseases may be considered an inherently ecological process involving intraspecific and interspecific interactions between vectors, pathogens, and host populations (Keesing et al. 2006). When human populations are implicated, pathogen transmission dynamics also involve socioeconomic, cultural, political, psychological, and ethical factors that pertain to the human dimension of disease (Spiegel et al. 2005; Briceño-León 2009; Ellis and Wilcox 2009). These factors may be classified as intrinsic or extrinsic to the human population (Ehrenberg and Ault 2005). Intrinsic factors are biological in nature (e.g., immune response) and can only be manipulated by advances in medical research and technology. Extrinsic factors include the environmental context, vector ecology and behavior, human activities, socioeconomic inequalities, and political factors, among others. These factors operate and interact at different scales within a complex system characterized by multiple interdependent components featuring feedback loops and nonlinear relations (Meadows 2008).

A thorough understanding of the combined effects of these factors is required to design more effective and sustainable disease control interventions (Charron 2012). Control interventions have traditionally been crafted in a reductionist biomedical approach, which argues that the sum of information provided by separately studying each component of the system is sufficient to understand disease transmission dynamics (El Sayed et al. 2012). Other more integrative approaches (ecohealth or eco-bio-social) focus on the interactions among multiple ecological, biological, and social factors and their combined effects on human health (Spiegel et al. 2005; Charron 2012). Social factors include large-scale forces such as poverty and social inequality; land tenure and agricultural development; public and private services such as water supply, sanitation, and garbage collection; demographic change and urbanization; vector control programs and other healthcare services; and community- and household-based knowledge, attitudes, and practices. The more integrative approaches pursue the design and implementation of sustainable, cost-effective disease control strategies to reduce social- and gender-associated inequalities related to health (Charron 2012; WHO 2008).

Chagas disease, caused by the protozoan *Trypanosoma cruzi* and mainly transmitted by triatomine bugs, is a major neglected tropical disease and a serious cause of human chronic disease in the Americas (WHO 2015). All triatomine species and mammals appear to be susceptible to the infection. Triatomine bugs are obligate hematophagous insects with opportunistic feeding habits on mammals and birds, and while doing so, they may contaminate their skin with urine or feces and transmit *T. cruzi* to mammalian hosts. The parasite may also be transmitted through food

items contaminated by sylvatic triatomine bugs or sylvatic hosts (e.g., opossums). Other transmission routes (vertical, transfusional, organ transplant) exist. Some triatomine species may also transmit other trypanosomatids (e.g., *Trypanosoma rangeli*) to humans and mammals through their bites; *T. rangeli* is considered non-pathogenic for its mammalian hosts.

Here we selectively review the biological, ecological, and social factors involved in the domestic transmission of *T. cruzi* (Fig. 1). We frequently provide examples related to the Southern Cone of South America and to its main vector *Triatoma infestans*, partly because this is where Chagas disease attained the greatest prevalence in humans (WHO 2015) and partly because of the wealth of information on *T. infestans*. We also examine how ecological and social factors contribute to human infection risk. We defer consideration of vector control measures and their impacts to a separate chapter. Disease-related aspects and spatial dynamics fall outside of the scope of this review.

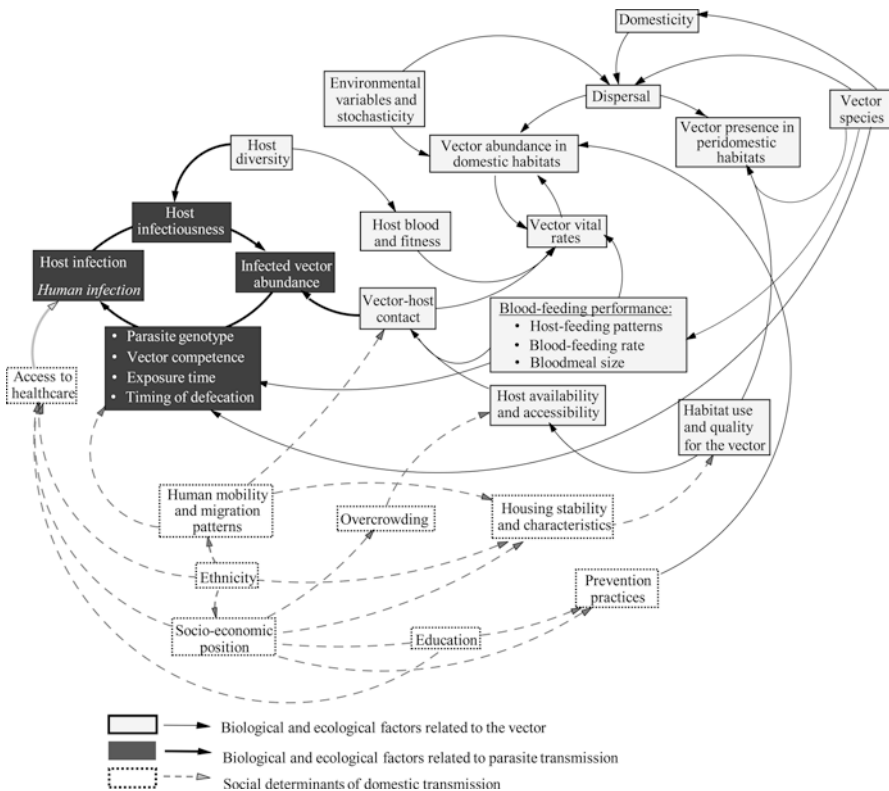


Fig. 1 Conceptual map of the relations between ecological, biological, and social factors affecting the domestic transmission of *T. cruzi*

2 Biological and Ecological Factors Related to the Vector

2.1 Species and Epidemiologic Relevance

Of the approximately 150 species of Triatominae (Heteroptera: Reduviidae) currently recognized, <10 species have become closely adapted to thrive in domestic premises and feed on humans and other domestic animals (i.e., domesticated), and < 20 species have been involved in the transmission of *T. cruzi* infection to humans (Gourbière et al. 2012). Noireau and Dujardin (2010) divided triatomines in domestic, domiciliary, intrusive, and sylvatic species based on their epidemiological relevance for transmission and control. Although several attempts have been made to classify triatomine species, the subject still remains controversial (e.g., Waleckx et al. 2015a; Abad-Franch 2016) (see chapter “Chagas Disease Vector Control” on vector control). In this chapter, “domestic or domiciliary” refers to the set of contiguous human sleeping quarters and rooms that share a continuous roof structure.

2.2 Domesticity and Vector Abundance

Domesticity conveys several selective fitness advantages related to stable habitats (more protected from exposure to climatic extremes, such as human dwellings and structurally similar outhouses) with a stable supply of hosts (humans and domestic or synanthropic animals), balanced by the costs of adaptation to diverse types of habitats, blood-feeding on domestic hosts, and progressive genetic simplification (Dujardin and Schofield 2004). The immediate gains of domesticity translate into much larger triatomine population sizes than in sylvatic habitats, with additional benefits derived from human-mediated passive dispersal and an enlarged geographic range. Nondomestic triatomine species occupying peridomestic and sylvatic ecotopes are well adapted to cope with habitat instability.

Triatoma infestans expresses the extreme of the evolutionary trend toward domesticity (Dujardin and Schofield 2004), with widespread sylvatic foci only in Bolivia and Chile (see chapter “Chagas Disease Vector Control”). This dual feature is also shared by *T. dimidiata* in Central America versus Ecuador and by *Rhodnius prolixus* in Venezuela and Colombia versus Central America and southern Mexico. The intimate adaptation of *T. infestans* and *R. prolixus* to domestic habitats and epidemiological significance as vectors of human *T. cruzi* infection, combined with other technical aspects, justified launching regional elimination programs (WHO 2002).

Illustrating their relative success, the top domestic abundances recorded in a single human habitation reached 7900 (Rabinovich et al. 1979) to 11,403 *R. prolixus* (Sandoval et al. 2000a, b) and 8500 *T. infestans* over a 3-year period (Dias and Zeledón 1955). An enclosed experimental population of *T. infestans* in a hut of ~1 m³ with one chicken reached 15,844 insects (excluding eggs) 2 years after being

founded with 5 females and 3 males (Cecere et al. 2003). *Panstrongylus megistus* and *T. dimidiata* reach much lower densities than *T. infestans* or *R. prolixus*. The greater nutritional value of human blood adds an unappreciated advantage to domesticity (see Sect. 2.5).

Domesticity carries with it several implications. The stability/instability habitat divide connects with the large/small population size dichotomy, whether bug population dynamics are density-dependent or density-independent (and dominated by stochastic events such as weather, host death, and exposure to predators) and modify the effectiveness of vector control efforts (Sect. 2.6 and 2.7).

2.3 *Habitat Use and Quality for Triatomines*

A unified definition of habitat includes “the resources and conditions present in an area that produce occupancy—including survival and reproduction—by a given organism (Hall et al. 1997).” These include physical factors (such as temperature and moisture) and biotic factors (such as the availability of food and shelter and the absence of toxins or predators). This and other definitions of habitat supersede the notion that it merely represents physical space. Habitat use is considered selective if it is used disproportionately to its availability or, more in point, to its accessibility. Accessibility depends on interspecific interactions as well as social and environmental factors that might limit access to a given resource (Beyer et al. 2010). Although many triatomine species have characteristic habitat types with associated host species, the mechanisms underlying the observed habitat selection patterns remain mostly unknown.

Each triatomine species selects refuges for optimal conditions of temperature, relative humidity, and darkness at the microhabitat level (Lorenzo and Lazzari 1999; Lazzari et al. 2013) and marks suitable refuges via assembling factors present in their feces (Lorenzo and Lazzari 1996). These factors induced aggregation in nymphs of *T. sordida* and *T. infestans*, thus acting as a pheromone and kairomone (Lorenzo Figueiras and Lazzari 1998). Detailed site-level surveys before and after community-wide insecticide spraying in two rural areas of the Argentine Chaco have shown that sympatric triatomine species tended to occupy distinct peridomestic habitats (e.g., *Triatoma garciabesi* versus *T. guasayana* or *T. infestans*) or were positively associated both at site and house level (*T. sordida* and *T. infestans*) (Rodríguez-Planes et al. 2016, 2018). However, none of the secondary species were able to establish colonies and persist in domestic premises after the quasi-elimination of *T. infestans* despite recurrent invasion events (e.g., Rojas de Arias et al. 2012; Rodríguez-Planes et al. 2020).

Most assessments of habitat use have been derived from the frequency distribution of occurrence or relative abundance of triatomine bugs in field surveys. This information was used to rank the suitability of multiple habitats for a given species and to identify which of them may function as key sources of triatomines for house reinfestation after control interventions. For example, initial assessments of habitat

suitability for *T. infestans* in the Argentine Chaco were accomplished via surveys of habitat-specific infestation and bug abundance. These surveys suggested that chicken coops, goat corrals, and pig corrals were the most important ecotopes (López et al. 1999; Cecere et al. 2004, 2006, 2013; Gürtler et al. 2004; Ceballos et al. 2005). However, a broader survey measuring several fitness-related components in more habitat types showed that chicken coops and human sleeping quarters were relatively more important while goat corrals were at the other extreme (Gürtler et al. 2014b). These fitness components (sex ratio, female fecundity, nutritional status, and vector abundance) were in theory better descriptors of habitat suitability. Bug abundance and fecundity were aggregated across ecotopes, suggesting that bug population growth was concentrated in a few productive, high-quality sites.

These patterns are consistent with the 80-20 rule, by which approximately 80% of the vectors or disease cases would occur in 20% of the sample sites (Woolhouse et al. 1997). Using a different theory and methods, Taylor's law of fluctuation scaling described accurately the mean and variance of the habitat-specific abundances of four triatomine species in the Argentine Chaco, with slopes indicating spatial aggregation or variation in habitat suitability (Cohen et al. 2017). Both spatial aggregation and variation in habitat suitability are relevant for improved vector control and surveillance. Extending these approaches to other triatomine species and settings may provide new perspectives on their high-quality habitats.

One dimension of habitat quality relates to physical structure. Housing design and construction materials combined with their degree of maintenance determine the availability of refuges for domestic bugs, such as cracked walls, tiled or thatched roofing, and earthen floors (Dumonteil et al. 2013; Bustamante et al. 2014), affect the susceptibility of a house to bug invasion and subsequent colonization (Monroy et al. 2009), and may modify the effectiveness of insecticide applications (Gürtler et al. 2004; Cecere et al. 2013). The surface structure of indoor walls (unplastered or with many crevices) and the existence of thatched roofs were significant predictors of domestic infestation and abundance of the main domestic vectors of *T. cruzi* (Cecere et al. 1998; Mott et al. 1978a; Rojas de Arias et al. 1999; Andrade et al. 1995).

Experimental evidence showed that bug population size increased steadily with refuge availability over a 2-year period, with two out of three bug populations in low-refuge huts becoming extinct (Cecere et al. 2003). However, the exact way in which housing quality affects domestic infestation may vary between triatomine species. Dirt floors are highly important for *T. dimidiata* as it uses dirt for camouflage (Zeledón and Vargas 1984; Bustamante et al. 2014) but appear to be of little utility to *T. infestans*, which lacks a camouflage behavior. Dirt floors are indicators of high social vulnerability and frequently are associated with other household features favoring house infestation and triatomine abundance, e.g., mud walls and overcrowding (Fernández et al. 2019a). Window screens greatly reduced the domestic invasion of *T. dimidiata* in Yucatan, Mexico (Waleckx et al. 2015b). Peridomestic structures also provide numerous shelters, as in chicken houses and animal enclosures built with mud, wood, rock, or piled thorny shrubs (Carcavallo et al. 1999; Cecere et al. 2004; Walter et al. 2007; López et al. 1999; Diotaiuti et al. 2000; Gurevitz et al. 2013; Ramsey et al. 2003). If bug-proof chicken houses replaced the

current structures used in northeast Argentina, *T. infestans* and *T. sordida* would lose a key productive habitat (Gurevitz et al. 2013; Rodriguez-Planes et al. 2018). In general, peridomestic structures function as host and triatomine breeding sites and serve as sources of insects that invade human habitations (Cecere et al. 2004, 2006).

2.4 Host Availability

Host availability is quantified by the local abundance of avian or mammalian hosts. However, a host may be available but not accessible if host-seeking triatomines cannot actually feed on it because of some actual or virtual barrier (e.g., bednets, repellents, distance). In domestic habitats, the most frequent hosts of triatomine bugs are humans, dogs, cats, chickens, and rodents. Domestic bug abundance increased with increasing numbers of human residents in rural communities infested with *T. infestans*, *P. megistus*, *R. prolixus*, or *T. dimidiata* (Marsden et al. 1982; Piesman et al. 1983; Gurevitz et al. 2011; Campbell-Lendrum et al. 2007). Moreover, the presence of indoor-resting chickens and dogs correlated positively with domestic bug abundance across settings and species (e.g., Lardeux et al. 2015; Dumonteil et al. 2013; Bustamante et al. 2009, 2014; Cecere et al. 1998; Gurevitz et al. 2011). These relationships tend to be consistent with the outcome of domestic triatomines' blood meal surveys (Sect. 2.5).

Host demography and domestic animal management practices add another dimension to the links between host availability/accessibility, vector abundance, and socioeconomic position, as the habits of keeping chickens indoors for protection and letting domestic dogs wander freely or share domestic premises are frequent in rural areas under a subsistence economy. For example, in typical rural villages of the Argentine Chaco, seasonal breeding pulses determine a surge of host numbers with the appearance of juveniles and their enhanced exposure to triatomines. The occurrence of indoor-nesting chickens peaked in spring and decreased during the hot summer months toward reaching a minimum over fall-winter (Cecere et al. 1997). Permanent chicken coops were rare and nesting sites relatively instable over time; in the absence of the host, the starved bugs presumably dispersed and generated new foci. The household number of chickens varied widely over time depending on household acquisition, consumption, and disease outbreaks (Rodríguez-Planes et al. 2018). In goat corrals, kids kept enclosed for protection were continually exposed to triatomines, while adult goats were allowed to roam and forage the little grass available in the dry Chaco (Ceballos et al. 2005). The population size of domestic dogs remained stable from year to year though with high turnover rates (Gürtler et al. 1990). These fine-scale spatial and temporal heterogeneities affect triatomine vital rates and population size.

Host behavior patterns also affect host accessibility. Although household size varies little from year to year, in practice householders exposed to hot weather or nuisance pests move their beds and hammocks to open air as an adaptive response (see Sect. 2.5) and thus may become less accessible to domestic triatomines

(Rabinovich 1985; Gürtler et al. 1997; Brenière et al. 2017). In doing so, however, householders may become more exposed to peridomestic or sylvatic vectors such as *R. pallescens*. Households also differed in letting domestic dogs and cats roam freely for all or part of their food. Dogs have a marked crepuscular free-ranging behavior, and male dogs wander in small packs at night during estrus periods (Matter and Daniels 2000). In rural areas throughout Latin America, it is quite common that dogs are not neutered. These host activity patterns may reduce the likelihood of host-vector encounters. Thus, scoring the actual presence or absence of domestic hosts (past and current) presents special challenges. Site-level occupancies may vary widely over time depending on weather, host behavior, biting insects, and cultural patterns. Triatomines may respond fast to the sudden absence of a host and actively disperse (Castillo-Neyra et al. 2015).

2.5 Blood-Feeding Performance

Host-Feeding Patterns The host-feeding patterns of Triatominae are key to understanding the eco-epidemiology of Chagas disease. Most species of Triatominae show eclectic blood-feeding patterns on birds and mammals (Wisnivesky-Colli 1987; Rabinovich et al. 2011), with very few triatomine species displaying a remarkable specificity for a host species (e.g., *C. pilosa* for bats in caves) (Dujardin and Schofield 2004). Some triatomine species may occasionally feed on reptiles, on amphibians, and on insect hemolymph. The small nymphs may even feed on blood-engorged conspecifics (cleptohematophagy). In domestic habitats, the main blood meal sources of triatomine bugs are humans, dogs, chickens, and cats. House mice and rats are also a relevant blood meal source for domestic populations of *T. dimidiata* and *Triatoma barberi* (De Urioste-Stone et al. 2015).

The species of Triatominae with significant public health relevance are those that feed on humans or which may contaminate foodstuffs. Table 1 identifies 24 species of Triatominae with documented evidence of having fed on humans as determined by immunologic methods, estimated from the data compiled by the most recent review on triatomine blood-feeding patterns (Rabinovich et al. 2011). From the 159 data sets, we selected those that included any species collected in domestic habitats only, or in domestic or peridomestic habitats only, and excluded all other habitat sources. The selected list includes 68 studies and 28,054 specimens tested.

The degree of human-vector contact, measured by the average human blood index (i.e., the fraction of tested insects having a human blood meal), peaked in *R. prolixus* (79.2%), *R. pallescens* (65.0%), *T. pallidipennis* (44%), *T. infestans* (40.3%), and *P. megistus* (36.6%). A second group of species had a mean human index between 10% and 20% (*P. herreri*, *T. barberi*, *R. pictipes*, *T. vitticeps*, *R. ecuadoriensis*, *T. dimidiata*, *T. brasiliensis*, and *T. pseudomaculata*). Chickens ranked high, followed by dogs and cats. The rodent blood index averaged 17.1% across all species in the list and frequently exceeded 40%. Even sylvatic populations of

Table 1 Host-feeding patterns of Triatominae collected in domestic or peridomestic habitats

Species	No. of studies	No. of insects tested	Human blood index		Dog blood index		Cat blood index		Chicken blood index		Rodent blood index	
			Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
<i>R. prolixus</i>	6	517	79.2	18.8	6.3	4.8	9.3	19.1	3.3	5.3	0.3	0.8
<i>R. pallidus</i>	2	1391	65.0	18.4	1.0	1.4	0.5	0.7	9.0	7.1	6.0	4.2
<i>T. pallidipennis</i>	1	18	44.0	6.0			0.0	0.0			6.0	
<i>T. infestans</i>	11	5134	40.3	20.5	11.9	11.1	9.0	5.0	22.2	10.1	4.6	8.7
<i>P. megistus</i>	7	5728	36.6	31.7	4.9	1.5	3.9	6.5	30.7	20.0	5.3	6.2
<i>P. herrerii</i>	1	77	21.0	8.0			1.0	16.0			55.0	
<i>T. barberi</i>	2	958	20.5	3.5	7.0	1.4	7.0	1.4	10.0	0.0	47.5	3.5
<i>R. pictipes</i>	1	10	20.0	20.0			10.0	30.0			20.0	
<i>T. vitticeps</i>	1	79	14.0	11.0			0.0	11.0			4.0	
<i>R. ecuadoriensis</i>	1	8	13.0	0.0			0.0	50.0			25.0	
<i>T. dimidiata</i>	5	933	11.2	8.1	13.0	11.3	1.0	1.4	23.0	23.4	39.8	44.1
<i>T. brasiliensis</i>	2	1196	11.0	15.6	3.0	4.2	4.5	6.4	75.0	25.5	1.5	2.1
<i>T. pseudomaculata</i>	2	3789	10.5	13.4	7.5	9.2	2.0	0.0	59.0	22.6	12.0	15.6
<i>T. rubrofasciata</i>	2	548	9.5	4.9	22.5	0.7	0.5	0.7	3.5	2.1	47.5	2.1
<i>T. rubrovaria</i>	2	153	6.0	4.2	0.0	0.0	0.0	0.0	8.0	11.3	6.5	4.9
<i>T. sordida</i>	14	6703	5.4	6.0	5.1	6.7	0.6	1.1	58.5	19.7	12.5	7.2
<i>P. lutzi</i>	1	79	4.0	0.0			1.0	32.0			28.0	
<i>R. nasutus</i>	1	135	4.0	2.0			0.0	93.0			0.0	
<i>T. maculata</i>	1	52	4.0	0.0			8.0	73.0			15.0	
<i>B. ferroae</i>	1	121	1.0	3.0			0.0	0.0			4.0	
<i>R. neglectus</i>	1	181	1.0	2.0			0.0	75.0			13.0	
<i>P. herrerii</i>	1	76	0.0	0.0			0.0	0.0			0.0	
<i>P. geniculatus</i>	1	2	0.0	50.0			0.0	50.0			0.0	
<i>T. costalimai</i>	1	166	0.0	0.0			0.0	16.0			58.0	

Summary estimates for humans and domestic or synanthropic animals from data compiled by Rabinovich et al. (2011)

T. infestans had human blood meals (Buitrago et al. 2013, 2016), as did sylvatic *Mepraia spinolai* (Brenière et al. 2017) and *T. sanguisuga* (Waleckx et al. 2014). Many other species have been reported to attack humans in the wilderness, such as *R. brethesi*, *T. guasayana*, and *T. brasiliensis*. In summary (i) many triatomine species other than the main domestic vectors blood-feed on or may attack humans under the appropriate circumstances; (ii) the rates of human-vector contact largely differed between and within species, habitats, and settings; (iii) the recorded patterns are fraught with a putative selection bias, as there is sparse information for the great majority of triatomine species; and (iv) mixing domestic and peridomestic bug collections deflates human blood indices and increases chicken blood indices, for example. The fact that triatomine host-feeding patterns are seldom related to local host numbers (i.e., at site or house level), host, and vector infection hampers the full understanding of system dynamics.

The host-feeding choices of hematophagous insect vectors are affected by the host species composition in a given habitat, relative host abundance, host proximity, and host defensive behavior (Lehane 2005). Host proximity has usually been considered more important than any intrinsic host preference for a host-seeking bug (Minter 1976). However, there were very few controlled host choice experiments in Triatominae. For *T. sordida* (typically associated with birds), first-instar nymphs significantly preferred birds to humans (Rocha e Silva et al. 1977), whereas the feeding success and blood meal size of fifth-instar nymphs were significantly larger on guinea pigs than on pigeons (Crocco and Catalá 1997). In laboratory-based trials, four caged vertebrate host species were simultaneously exposed to separate groups of fifth-instar nymphs of *T. infestans*, *T. dimidiata*, and *R. prolixus* (Jirón and Zeledón 1982); none of these species displayed definite host-feeding preferences among dogs, chickens, and opossums, but toads were rarely selected. Dogs were highly preferred over chickens or cats in host choice experiments conducted in small huts where the released bugs could choose to feed on any of the two host species available (Gürtler et al. 2009). Bugs that fed on dog engorged significantly more than bugs that fed on chicken or cat, suggesting dogs were more tolerant to bites than chickens or cats. These results were mainly consistent with field host-feeding patterns.

Host defensive behavior in response to triatomine bites determines the selective utilization of some host species and individuals (Kelly and Thompson 2000). Several triatomine species displayed negative density-dependent engorgement rates on non-anesthetized, unrestrained small chickens, pigeons, and rodents in laboratory settings (Crocco and Catalá 1997; Rabinovich 1985; Piesman et al. 1983; Schofield 1982). In the host choice trial described above, high vector densities tended to increase the shifts between hosts and significantly increased post-exposure bug weight though not to a large extent (Gürtler et al. 2009).

These basic processes combined with the rather limited dispersal range of Triatominae (especially of nymphs) determine that their host-feeding patterns tend to be spatially structured according to habitat type and correlate closely with the main local resident host(s). In rural villages in northwestern Argentina, the main or only blood meal sources of *T. infestans* in chicken coops, goat corrals, and pig

corrals were chickens, goats, and pigs, respectively (Gürtler et al. 2014b). The domestic populations of *T. infestans* displayed seasonal variations in feeding patterns related to the shifting resting sites of hosts during the hot season (Gürtler et al. 1997). In spring-summer domestic bug collections, the human blood index decreased substantially with the increasing presence of chickens or dogs indoors and also decreased with increasing domestic bug abundance, reflecting changes in human exposure. Moreover, the dog blood index increased significantly with increasing numbers of dogs and with domestic bug abundance and decreased as the chicken blood index rose. The presence of indoor-resting chickens correlated positively with domestic bug abundance and with an increasing chicken blood index (Cecere et al. 1997). Underlying these patterns are the opportunistic nature of host choice (expressed in high rates of mixed blood meals on different host species) and the spatiotemporal variations in host availability and accessibility. The inverse relationship between the human and chicken blood indices in domestic *T. infestans* was verified in at least two other rural settings in northern Argentina (Gürtler et al. 2014a; Ordóñez-Krasnowski et al. 2020). Host shifts affected domestic transmission (see Sect. 3.6).

Host Blood and Fitness The question on whether host blood type affects the fitness of triatomines has implications for understanding domesticity, population growth, and transmission risks. Host blood effects are well known in mosquitoes and tsetse flies (Lehane 2005) and affected the vital rates and engorgement levels of triatomines (Gardiner and Maddrell 1972; Núñez and Segura 1987). Human blood was better than sheep blood for vitellogenesis, general metabolism, and development in *R. prolixus* (Valle et al. 1987). Cohorts of *R. prolixus* that fed artificially on citrated blood during their entire lives in the same artificial environment achieved faster development rates and much larger blood meal size, body weight, and female fecundity when fed on human or rabbit blood rather than when bugs fed on chicken, sheep, or horse blood (Gomes et al. 1990). Avian blood usually has much lower hemoglobin and plasma protein than the blood of clinically healthy mammals and hence appears to be nutritionally inferior. However, the lower blood viscosity of avian blood allows increased ingestion rates and would reduce the risk of host-induced death (Lehane 2005). Goat (or sheep or cow) blood reduced the feeding efficiency of *T. brasiliensis* because triatomines are unable to agglutinate cattle erythrocytes (Araujo et al. 2009). Gardiner and Maddrell (1972) reported that *R. prolixus* bugs tended to blood-feed much less or not at all on adult goats or sheep that had been exposed repeatedly to bites (i.e., developed acquired resistance) and hence laid fewer eggs. This suggested that the rather large field populations of *T. infestans* in goat corrals most likely thrived at the expense of the immunologically naïve kids (Gürtler et al. 2004, 2017). When suitable hosts are not available, goat corrals become sources of dispersing triatomines as their nutritional state declines.

Blood-Feeding Rate and Blood meal Size These parameters affect the vital rates of triatomine bugs, including their propensity to initiate flight, the regulation of local population size (Schofield 1994), and parasite transmission rates. There are

few estimates of the blood-feeding rates, blood meal sizes, and nutritional status of Triatominae in field settings (reviewed in Gürtler et al. 2014b). Preliminary estimates of the feeding rates of domestic *T. infestans* and *R. prolixus* based on the distributions of body weight and body length yielded 5–8 to 5–20 days, respectively (Schofield 1980; Rabinovich et al. 1979). By measuring the temperature-adjusted occurrence of transparent urine assessed shortly after capture in experimental chicken coops, the blood-feeding rate of *T. infestans* proved to be temperature- and bug density-dependent (Catalá 1994). Domestic populations of *T. infestans* blood-fed every 3–4 days over the spring-summer period (Catalá et al. 1997; Gürtler et al. 2014a). Mean feeding intervals varied widely across ecotopes and peaked in chicken coops (López et al. 1999; Ceballos et al. 2005; Gürtler et al. 2014b). Some triatomine species may feed every 2 days in the insectary and withstand prolonged starvation over several months.

The only field estimate of blood meal size comes from experimental chicken houses stationed outdoors (Catalá 1994). The total blood meal contents of recently fed triatomines may be used as a proxy of blood meal size under assumed steady-state conditions (Gürtler et al. 2017). Human- and chicken-fed *T. infestans* had significantly larger blood contents than bugs fed on other hosts, whereas goat-fed bugs ranked last, in consistency with their average blood-feeding rates. Female fecundity was also maximal in chicken-fed bugs from chicken coops and minimal in goat-fed bugs. The greater blood-feeding performance and nutritional status of bugs from chicken coops, closely followed by domestic bugs, reflected in their having a larger body length than other peridomestic bugs across most life stages – a clear indication of habitat-associated fitness advantages.

Timing of Defecation Blood meal size determines the timing of defecation and hence the chance of eventual skin contamination with triatomine feces (Kirk and Schofield 1987; Trumper and Gorla 1991). Blood meal size and the timing of defecation were both inversely density-dependent. As host irritation increases, its defensive reactions lead to interrupted (smaller) blood meals and prolong the time to the first fecal drop. These mechanisms supported the hypothesis that the greatest chances of transmission of *T. cruzi* would occur at low bug densities. However, it does not necessarily follow from the above experiments that a feeding contact with a single bug at high bug population density has a lower risk of transmitting infection to an uninfected mammalian host than a feeding contact with a single bug at a low bug population density (Cohen and Gürtler 2001). The time needed to secure a replete blood meal and the timing of defecation differed substantially among the main triatomine vectors (Zeledón et al. 1977); both *T. infestans* and *R. prolixus* defecated during or shortly after blood-feeding while on the host. Although the North American species of Triatominae were once considered poor vectors based on their long defecation times, subsequent studies revealed that several of them would be efficient vectors (Zeledón et al. 2012).

2.6 *Environmental Variables*

Temperature and precipitation affect the geographic distribution of Triatominae (Gorla and Noireau 2017), their host-seeking and metabolic rates, body size, and vital rates. Before the onset of large-scale insecticide spraying campaigns in Argentina during the 1960s, house infestation with *T. infestans* occurred in areas where daily maximum temperatures exceeded 20 °C and vapor-pressure deficits were greater than 1100 hectopascals over at least 220 days a year (Curto de Casas et al. 1999). The minimum temperature of the coldest month apparently defined the geographic range of *T. infestans* and *R. prolixus*, the latter being also influenced by precipitation-related variables (Medone et al. 2015). At finer scales, triatomines are affected by variable microsite conditions. Different species display specific patterns of thermopreference and hygropreference that vary substantially over the feeding and daily cycles and affect refuge selection (Lazzari et al. 2013). For example, both egg hatching and molting success are severely reduced by very low relative humidity.

Environmental variables interact with habitat structure to generate heterogeneous microsite conditions. The domestic and peridomestic habitats of *T. infestans* damped external temperatures to different extents depending on their physical structure, ranging from a minimum in thorn shrub-fenced goat corrals to a maximum in typical mud-and-thatch human habitations (Vazquez-Prokopec et al. 2002). In general, bugs from animal enclosures with little capacity to dampen climatic extremes are exposed to increased risks of hyperthermia and desiccation, which likely trigger dispersal. Large swings in diurnal temperature prolong insect development times, reduce survival and female fecundity relative to constant temperatures (Nijhout et al. 2014), and reduce body size when temperatures reach stressful levels (Colinet et al. 2015). In contrast, goat corrals with thick fences made of piled shrubs and goat dung have a large damping capacity and are able to sustain large triatomine populations despite harsh winters (Schofield 1985). Thus, the exact physical structure of the habitat rather than its main function or host determine whether local conditions are suitable for triatomines.

2.7 *Population Dynamics and Vital Rates*

Nearly all the available information on triatomine survival, fecundity, and development rates comes from laboratory-reared cohorts held under optimal, constant conditions (e.g., Rabinovich 1972; Perlowagora-Szumlewicz 1975; Rabinovich and Feliciangeli 2015). Triatomine populations are stage-structured and have long life cycles (from 4–6 to 12 months or more). The most realistic approximations to field settings were provided by experimental bug populations kept in huts that mimicked typical rural houses exposed to the temperate climate of central Argentina. The huts were caged with mosquito netting to prevent in- or out-migration and housed either two or four chickens in structurally homogeneous huts (Gorla and Schofield 1989;

Gorla 1991) or one chicken under a three-level gradient of refuges (Cecere et al. 2003).

In these experimental systems, the population abundance of *T. infestans* fluctuated seasonally following temperature variations and peaked once in early- or mid-summer, as in rural houses from Brazil (Dias 1955; Schofield 1980). These populations displayed two peaks of adult emergence of differing intensity (Cecere et al. 2003; Gorla 1991) and peak numbers of eggs per female lagging by 1 month. During spring-summer, fecundity averaged approximately three eggs per female per day in huts with two to four chickens (Gorla and Schofield 1989) and in huts with maximum refuge availability and one chicken (Cecere et al. 2003). These estimates are lower than the average fecundity of *T. infestans* (4.07 eggs per female per day) fed twice a week and kept under optimal conditions (Núñez and Segura 1987). Both female fecundity and nymphal development rates steadily increased with increasing temperature above 16 °C (the threshold for development), whereas mortality was mainly determined by monthly mean minimum temperatures (Gorla 1992). A stage-structured stochastic model of the population dynamics of *T. infestans* described well the temperature-dependent seasonal variations in bug abundance, stage structure, and the two peaks of female fecundity rates and total egg numbers observed in hut experiments (Castañera et al. 2003).

In the experimental huts, the egg-to-adult mortality of *T. infestans* ranged from ~98.5% (Gorla and Schofield 1989) to 94.8–97.6% (Cecere et al. 2003) and exceeded a preliminary estimate for domestic *T. infestans* (86.3%) based on the recovery of dead bugs and exuviae (Schofield 1980). In one of the studies (Cecere et al. 2003), a founder female had a maximum life span of 20 months, and the average for adult males (7.8) and females (5.6) exceeded other estimates of 4–5 months (Gorla and Schofield 1989). Bug mortality was density-independent, and female fecundity was weakly density-dependent (Gorla and Schofield 1989; Gorla 1991). Domestic populations of *R. prolixus* also failed to display density-dependent mortality (Rabinovich 1985). Chickens most likely were a refuge-dependent mortality factor: both nymphs and adults from huts with plastered walls had lower survival rates than bugs from maximum-refuge huts (Cecere et al. 2003). In the absence of migration, the net reproductive rate (R_0) decreased steadily from 3.91 to 0.25 in maximum- to minimum-refuge huts, respectively (Cecere et al. 2003). Schofield (1980) estimated $R_0 = 8.7$ by combining laboratory and field data for domestic *T. infestans*. Rabinovich (1972) estimated $R_0 = 25.04$ for laboratory-reared cohorts of *T. infestans* having very large survivorship and very low fecundity. These estimates of R_0 reflect the species' large capacity for establishing new foci and for population recovery following insecticide treatment.

Insecticides are a major source of bug mortality even when they are applied by householders. In the absence of government-sponsored insecticide campaigns, domestic bug abundance was negatively related to the domestic application of insecticides carried out by householders (Gurevitz et al. 2011; Gaspe et al. 2015). With increasing access to insecticides, especially in agricultural settings, the population size of domestic triatomines may rarely reach the typical high levels recorded in the past at which density-dependent effects on vital rates may set in. Rather,

domestic bug populations may be held at the lower limits imposed by insecticide use, housing improvements, and environmental stochasticity. These smaller bug populations occupying discrete patches connected by frequent active dispersal (zu Dohna et al. 2009), subject to stochastic events, may dominate the current and future eco-epidemiological scene.

Dispersal plays a key role in the invasion of domestic premises and establishment of new colonies, the recovery of bug population size after control interventions, and the spatial structure of triatomine populations. It may also contribute to the regulation of local population size, as suggested by the density-dependent loss of marked adult *R. prolixus* from domestic premises (Rabinovich 1985). In contrast, flight initiation was inversely related to *T. infestans* density in a laboratory setting (McEwen et al. 1993), suggesting that other processes may be implicated (e.g., pheromone-mediated searches for mates).

The dispersal of triatomine bugs is accomplished by active (walking, flight) or passive means via carriage in clothes, luggage, and firewood or as eggs stuck to the feathers of some birds (Schofield 1994). Passive transport of domestic triatomines is always a possibility, as shown by the finding of a *T. infestans* adult further south of its historical geographic range (Piccinali et al. 2010). Flight dispersal is limited to a few 100 m up to a few km, whereas passive dispersal has been associated with the long-distance range expansion of *T. infestans* to northeast Brazil, *R. prolixus* to Central America, and *T. dimidiata* to Ecuador. Mark-recapture studies demonstrated an intense exchange of nymphs and adults of domestic *R. prolixus* between houses located 100 and 500 m apart, consistent with its well-known flight capacity (Rabinovich 1985). The flight range of *T. infestans* (considered a poor flier) may exceed 2400 m, as suggested by sustained tethered flights at speeds of 2 m/s for at least 20 min (Ward and Baker 1982). Walking dispersal of nymphs and adult bugs may play a substantial role in establishing new foci at finer scales and contribute to the spatial aggregation of infestation (Vazquez-Prokopec et al. 2006; Abrahan et al. 2011). It may also explain the finding of human-fed triatomines in nearby peridomestic habitats not used as human resting sites (Cecere et al. 1997; Gürtler et al. 2014b).

Flight dispersal invariably includes unfed triatomines and occurs within the first 2–3 h after sunset in most of the species investigated (Di Iorio and Gürtler 2017). The initiation of flights is usually triggered by starving conditions (reflected in low body weight-to-body length ratios) and mean temperatures in the range from 20 to 30 °C. The duration and detailed time structure of the dispersal season are relevant because they determine subsequent establishment events and eventual human exposures. Analysis of a long time series of site infestations in a rural village suggested increased dispersal of *T. infestans* during spring and a 6-month lag between a new bug establishment on a site and dispersal from this site (zu Dohna et al. 2009).

Artificial light sources usually attract adult triatomines of many species and favor house invasion. Public streetlights were positively and significantly associated with domestic infestation with *T. dimidiata* in Yucatan, Mexico (Pacheco-Tucuch et al. 2012). When the streetlight posts of a small village in western Argentina were systematically inspected for triatomines between sunset and midnight over

spring-summer, the occurrence of flight-dispersing triatomines (from four species) steadily increased between 16.6 and 31.7 °C, suggesting a putative temperature threshold for flight initiation at 17–18 °C (Di Iorio and Gürtler 2017). Although the catch of adult *T. infestans* at the streetlight posts was sex-independent, that of *T. guasayana* was strongly male-biased – a pattern that has been recorded elsewhere and in other triatomine species. In an experimental setting, male *R. prolixus* bugs increased substantially their takeoff activity in response to female pheromones, but the reverse did not occur (Zacharías et al. 2010). This suggests that a colonizing, unfertilized female triatomine may be able to recruit flight-dispersing males and thus increase the chances of establishing a viable bug colony. However, flight dispersal may also be female-biased, as suggested by field observations of individually marked adult *P. megistus* (Forattini et al. 1977) or *T. infestans* in open chicken coops and by microsatellite-based genetic studies (reviewed in Gürtler et al. 2014b). Sex-biased flight dispersal may contribute to imbalanced adult sex ratios across ecotopes (Payet et al. 2009).

3 Biological and Ecological Factors Related to Parasite Transmission

3.1 Parasite Diversity

Trypanosoma cruzi (Kinetoplastida: Trypanosomatidae) has a genetically diverse clonal structure classified into six genotypes (TcI–TcVI) denominated discrete typing units, or DTUs (Zingales et al. 2012). Whether TcBat, a recently described genotype mostly restricted to bats, is a different DTU is still under debate (Marcili et al. 2009; Zingales 2018). All DTUs are capable of infecting humans and mammals, and their geographical distribution and frequency of occurrence vary widely across the Americas (reviewed by Brenière et al. 2016). Humans and > 150 species of nonhuman mammalian hosts have been found naturally infected with *T. cruzi*; other vertebrates are refractory to the infection (Jansen et al. 2017).

Transmission Cycles Domestic and sylvatic habitats sustain two main types of transmission cycles (Miles et al. 2003). Sylvatic cycles involve sylvatic mammals and sylvatic triatomine species, whereas domestic cycles mainly include domestic triatomines, humans, and domestic or synanthropic animals. The two archetypical sylvatic cycles across the Americas are an arboreal cycle involving didelphid marsupials and TcI and a terrestrial cycle involving armadillos and TcIII (Yeo et al. 2005; Brenière et al. 2016). However, these associations are not absolute. TcI has the broadest distribution from southern United States to Argentina and Chile. It has been mainly found in sylvatic cycles across the Americas and in domestic cycles to the north of the Amazon basin. TcII has been mainly associated with domestic cycles but has also been isolated from sylvatic mammals. TcV and TcVI predominate

in domestic cycles across the Southern Cone countries. TcBat, TcIII, and TcIV have been mainly found in sylvatic cycles.

The degree of connectivity or overlap between domestic and sylvatic cycles may affect disease control and elimination efforts. If transmission cycles overlap, the introduction of sylvatic parasites may threaten efforts directed at curtailing domestic transmission, as recorded in Mexico (Ramsey et al. 2012). Overlapping transmission cycles of TcI and TcVI were also recorded in Yucatan, Mexico (López-Cancino et al. 2015), Guatemala (Pennington et al. 2015), and Venezuela, where *Rhodnius* bugs infested both houses and palm trees (Miles et al. 2003). A classic example of separate transmission cycles occurred in Bahia, Brazil, where TcII circulated in houses infested with *P. megistus* while TcI circulated between *T. tibiamaculata* and *Didelphis albiventris* opossums in bromeliad epiphytes (Miles et al. 2003). Separate transmission cycles occurred in the Argentine Chaco region, where TcV/TcVI predominated in domestic habitats while TcI and TcIII were restricted to sylvatic hosts (Cardinal et al. 2008; Diosque et al. 2003; Macchiaverna et al. 2015, 2018; Orozco et al. 2013; Enriquez et al. 2013; Lucero et al. 2016).

3.2 Domestic Reservoir Hosts

Nonhuman Reservoir Hosts Dogs, cats, rodents, and domesticated guinea pigs are major domestic nonhuman reservoir hosts of *T. cruzi* (reviewed in Gürtler and Cardinal 2015). They are able to maintain *T. cruzi* in the absence of any other host species and play key roles as amplifying hosts and parasite sources in many domestic or peridomestic transmission cycles across ecoregions and triatomine species. House mice and rats contributed to domestic bug infection with *T. cruzi* in many settings (Bustamante et al. 2014; Rosal et al. 2018). Community-based rodent control measures significantly reduced rodent infestations and the prevalence of *T. cruzi* infection in early-stage nymphs of *T. dimidiata* (De Urioste-Stone et al. 2015).

Human Hosts The prevalence of human infection with *T. cruzi* attests to the potential magnitude of the disease and to the size of the human reservoir. Humans constitute a many decade-long reservoir of *T. cruzi* unless an effective treatment is administered. In contrast, other nonhuman domestic reservoir hosts have large turnover rates, which combined with effective vector control actions produce a fast clearance of infected individuals, which are mostly replaced with uninfected ones (Gürtler et al. 1990; Gürtler and Cardinal 2015).

3.3 *Human Infection*

Humans typically acquire a vector-borne infection with *T. cruzi* while sleeping at night at their usual resting location or during short visits to other villages (Gürtler et al. 2007b). Incidental human infection may sporadically occur in campsites and as an occupational hazard (Brenière et al. 2017). Human exposure may eventually derive from infected triatomines dispersing from peridomestic outhouses (Cardinal et al. 2014) or from the interface with sylvatic habitats, as in the dry-shrub fences harboring *T. eratyrsiformis* in northern Argentina (Cecere et al. 2016), stone piles infested with *T. pallidipennis* in Mexico (Brenière et al. 2017), and palm trees with intrusive *Rhodnius* sp. and other triatomine species (Jácome-Pinilla et al. 2015; Abad-Franch et al. 2015). Human susceptibility to *T. cruzi* infection appears to be independent of age and gender.

The infection involves a short acute phase and a lifelong chronic phase and is irreversible unless the patient is treated with nifurtimox or benznidazole. A very small fraction of *T. cruzi*-seropositive individuals spontaneously revert to a seronegative status in the absence of etiologic treatment (e.g., Morillo et al. 2015). The death rate of untreated individuals during the acute phase ranged from 2 to 12% and was inversely related to patient age (Dias and Schofield 2017), as does the chance of a symptomatic presentation (Romaña 1963). A variable fraction (20–30%) of the survivors develop cardiac disease and suffer increased death rates between 35 and 50 years of age, especially males.

The bug-to-human transmission probability (b) is the probability that, in one feeding contact between one infected triatomine and an uninfected human, the human acquires a *T. cruzi* infection. Using indirect methods, b was estimated to range between 0.00026 and 0.0011 (Rabinovich et al. 1990; Nouvellet et al. 2013). Combined with vectorial capacity and other variables, b was used to estimate the threshold density of infected vectors required to initiate transmission chains and allow the infection to persist in the community. Vector control programs have extrapolated this rationale to the notion of a threshold domestic infestation prevalence associated with vector-borne transmission (Aiga et al. 2012). In practice, measuring each of the variables involved in vectorial capacity with any accuracy is fraught with major difficulties (Dye 1992). Several studies revealed the occurrence of prevalent or incident human cases at very low densities of *T. cruzi*-infected domestic triatomines per unit of search effort (Piesman et al. 1985; Rabinovich et al. 1990; Gürtler et al. 2005; Cardinal et al. 2018). Furthermore, the relation between bug population density and the probability of transmission by contamination during a single feeding contact with an infected bug is hard to assess empirically. Estimation of a threshold density of infected bugs for domestic transmission, if there is any, is additionally hindered by the low sensitivity and imprecision of triatomine sampling methods (Abad-Franch et al. 2014; Rojas de Arias et al. 2012) and human mobility (see Sect. 4.3).

3.4 *Host Infectiousness*

This key parameter has usually been measured by xenodiagnosis in at least three partially related forms, including the proportion of uninfected vectors that become infected after a replete blood meal on an infected host (i.e., host infectiousness), and more lately by real-time PCR (Gürtler and Cardinal 2015). Dog and cat infectiousness determined by xenodiagnosis correlated closely with the concentration of *T. cruzi* DNA determined by quantitative real-time PCR (Enriquez et al. 2014).

Before the implementation of large-scale control campaigns in southeast Brazil, the prevalence of xenodiagnosis-positive dogs (28.6%) and cats (19.7%) largely exceeded that recorded in humans (5.7%) (Freitas 1950). A similar ranking was often recorded in areas infested with *R. prolixus*, *T. dimidiata*, and *T. infestans* (Gürtler et al. 1996; Pifano 1973; Zeledón et al. 1975). Nearly all the triatomines that fed on human acute cases usually became infected regardless of the species or instar used (Minter-Goedbloed et al. 1978), whereas in a review of several studies *T. cruzi*-seropositive patients (presumably in the chronic stage) infected from 2–3% to 26% of xenodiagnosis nymphs (Gürtler et al. 1996). In a recent population-based survey, 60.5% of *T. cruzi*-seropositive humans were infectious to xenodiagnostic triatomines examined by optical microscopy and molecular methods; on average, they infected 5.2% of fourth-instar nymphs, and human infectiousness conformed to the 80-20 rule (Macchiaverna et al. 2020). The infectiousness of *T. cruzi*-seropositive people declined with age (Maguire et al. 1982), unlike the age-independent pattern frequently recorded in dogs from endemic rural areas (Gürtler et al. 1996; Enriquez et al. 2014). Moreover, the mean infectiousness of seropositive dogs to seropositive humans differed by an order of magnitude. Thus, although all mammalian species may be considered potential hosts of *T. cruzi*, their reservoir competence may differ substantially.

3.5 *Vector Competence*

All nymphal instars and adult stages of Triatominae are susceptible to *T. cruzi*, although perhaps not to the same extent, and may become infected with *T. cruzi* when feeding on an infected mammal carrying bloodstream trypomastigotes. The infection may rarely occur by coprophagy or cannibalism and is mostly irreversible except when the insects are severely starved. Following the infectious blood meal and a short latent period ranging from 2 to 10 days, the intensity of infection increases exponentially up to a maximum reached by 45–60 days postinfection when the bugs are fed regularly on noninfected hosts (Garcia et al. 2007). Parasite multiplication and development of metacyclic trypomastigotes in *T. infestans* was optimal between 23 and 27 °C, nil below 10 °C, and declined at 28 or 36 °C (Neves 1971), anticipating the strong seasonal forcing in human incidence of infection with *T. cruzi* (see Sect. 3.6). The intensity of bug infection varied both with parasite DTU

and triatomine species (Campos et al. 2007; Carvalho-Moreira et al. 2003; de Lana and de Menezes-Machado 2017). The interactions between *T. cruzi* and triatomines are affected by parasite strain, triatomine nutritional state, trypanolytic compounds, digestive enzymes, lectins, gut microbiota, and endocrine system (Garcia et al. 2007; Dumonteil et al. 2018).

The infection with *T. cruzi* reduced the life span of third-, fourth-, and fifth-instar nymphs of *T. infestans* by 14–17% when the insects were severely starved (Schaub 1992), decreased the fecundity and fertility of *R. prolixus*, increased bug mortality in a temperature-dependent way, and prolonged development (Elliot et al. 2015; Marlière et al. 2015; Guarneri and Lorenzo 2017). Whether *T. cruzi* affects the flight dispersal of *T. dimidiata* in a sex-dependent way requires further experimental research (Ramirez-Sierra et al. 2010).

In field settings, the cumulative chances of exposure to an infectious blood meal source are expected to increase over time or with increasing bug developmental stage and blood meal size; these increase the probability of ingesting at least one parasite and the total number of parasites ingested. Bug superinfections (i.e., a new *T. cruzi* infection of an already infected bug) may be quite frequent when the intensity of transmission is high. The prevalence of bug infection increased with bug stage, usually from third instars onward and reached maximum levels in fifth-instar nymphs or adult bugs (e.g., Albarracin-Veizaga et al. 1999; Cardinal et al. 2007, 2014). The intensity of *T. cruzi* infection in *T. infestans* also increased with each successive instar and peaked in late spring, including trypomastigote densities (Giojalas et al. 1990). Only 5–20 to 2000 metacyclic trypomastigotes are needed to experimentally infect a susceptible mouse via the conjunctival, oral, or contaminative cutaneous routes (Eickhoff et al. 2013).

3.6 Transmission Dynamics

Before the implementation of large-scale insecticide spraying campaigns in endemic areas, the seroprevalence of human infection with *T. cruzi* increased nonlinearly with age in stable populations subject to a rather constant risk of infection over time (Fig. 2). Simple catalytic models of pathogen transmission can be fitted to age-specific seroprevalence rates of infection to estimate the per capita rate at which a susceptible host acquired the infection in unit time over the age range covered by the curve (the force of infection) under several assumptions (Muench 1959; Nouvellet et al. 2015). Figure 2 shows the close fit of the irreversible catalytic model to seroprevalence data obtained in two areas of central Argentina in 1956 (Rosenbaum and Cerisola 1961). The force of infection was -0.041 per year (95% confidence interval, -0.0254 and -0.057) in Ojo del Agua, Santiago del Estero (Fig. 2a), and -0.045 (-0.053 and -0.037) in Elcano, Córdoba (Fig. 2b). Seroprevalence rates were predicted, and observed, to reach 100% in age groups >70 years; the 50% infection rates were reached by 20 years of age. More recent surveys also showed that nearly all old-age inhabitants were seropositive for *T. cruzi* in some rural

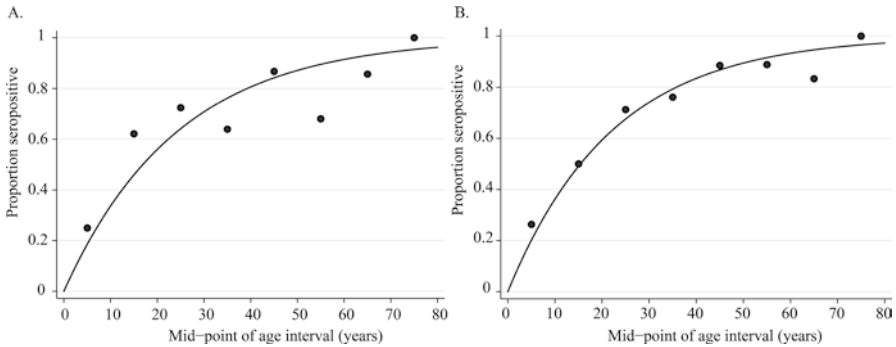


Fig. 2 Observed (dots) and expected (line) age-specific seroprevalence rates for *T. cruzi* infection in humans from Ojo de Agua (a) and Sebastián Elcano (b), Argentina, May 1956. Data taken from Rosenbaum and Cerisola (1961); seropositivity determined by a complement-fixation test. The line is the fit of the catalytic model with constant force of infection over time and age estimated as in Gürtler et al. (2005)

communities of the Bolivian Chaco (Samuels et al. 2013) and in indigenous communities of Santa Marta, Colombia (Mejía-Jaramillo et al. 2014). At least 50% of those aged >40 years were *T. cruzi* seropositive in the Argentine Chaco (Cardinal et al. 2018; Fernández et al. 2019b).

Before large-scale insecticide campaigns, most *symptomatic* acute cases occurred before reaching 15 years of age, but the distribution displayed a long tail extending up to 52 years of age, with no gender-related asymmetry (Romaña 1963). Figure 3 shows that while the expected seroprevalence of *T. cruzi* infection increased with increasing age in the absence of control actions, the observed frequency of *symptomatic* acute cases declined fast with age, although some occurred even after 50 years of age.

Following the implementation of control actions, the observed seroprevalence rates can be compared with those predicted by other candidate models to infer whether the efforts had effectively diminished the force of infection and by how much (Cardinal et al. 2007; Cucunubá et al. 2017; Feliciangeli et al. 2003; Nouvellet et al. 2015; Samuels et al. 2013).

Seasonality strongly affects the intensity of transmission of *T. cruzi* in subtropical and temperate areas. The incidence of *symptomatic* human cases of Chagas disease displayed similar seasonal variations in northern Argentina across four decades (Romaña 1963; Rebololán and Terzano 1958; Ledesma Patiño et al. 1992; Lugones et al. 1994). Incidence steeply rose from nonzero minimum values in August (cold season) to peak by November (late spring) and then slightly decreased during the hot summer months (Fig. 4). The relative rate of change in the frequency of acute cases increased faster from late winter to spring than at other times in three of the four data sets. A similar pattern occurred in central Brazil in the 1950s (Schofield 1994). These patterns closely match seasonal variations in temperature acting on triatomine blood-feeding rates (Fig. 5).

Fig. 3 Expected seroprevalence for *T. cruzi* (estimated through an irreversible catalytic model with force of infection = 0.02 per year, line) and the observed frequency of symptomatic acute cases of human Chagas disease (dots) in Tucumán, Argentina. Data taken from Romaña (1963)

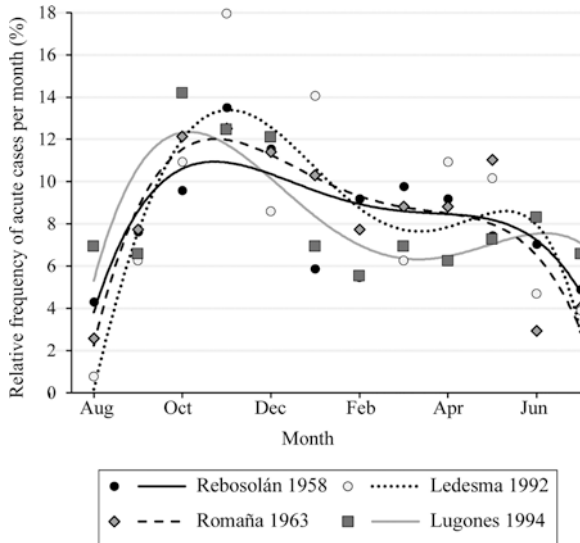
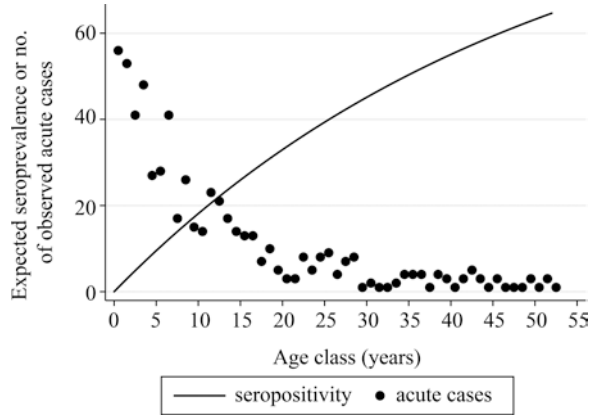


Fig. 4 Monthly-specific relative frequency of symptomatic acute cases of Chagas disease in humans from Tucumán and Santiago del Estero, Argentina. Data taken from Rebololán and Terzano (1958), including 511 cases diagnosed over 1947–1956; Romaña (1963), including 272 cases; Lugones et al. (1994), including 289 cases, and Ledesma Patiño et al. (1992), including 128 cases over a 3-year period ca. 1990. The lines are the fit of a four-degree polynomial model. All time series start at the all-time minimum values recorded in August

The relations between domestic host availability, bug abundance, and blood-feeding behavior described above, in interaction with local host infection and infectiousness, determine household-level variations in the prevalence and abundance of domestic bugs infected with *T. cruzi*. The strong and positive association between household infection (especially children) and the presence or abundance of infected *T. infestans* or *P. megistus* has been documented across multiple settings (Mott et al.

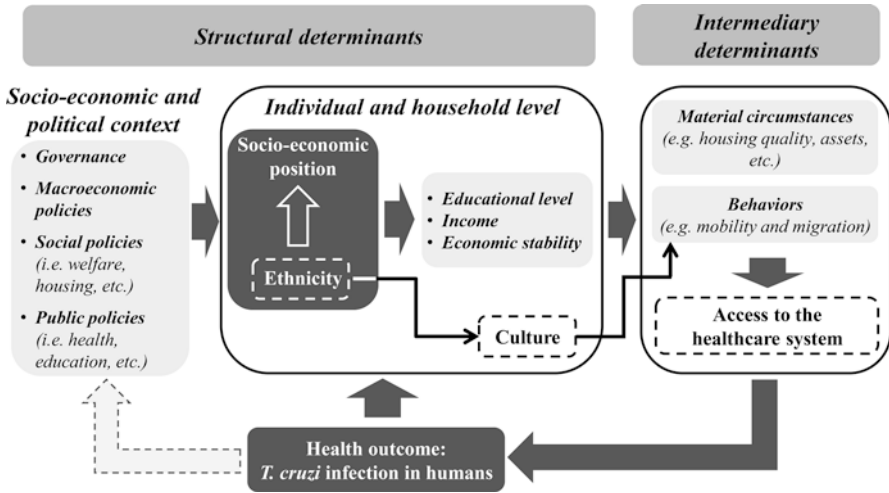


Fig. 5 Conceptual framework for the social determinants of health (SDHs) applied to Chagas disease. Adapted from Solar and Irwin (2010). The structural determinants are differentiated between those related to the socioeconomic and political context at national or regional levels and those pertaining to the individual and household level, as are the intermediary SDHs. The dashed light gray arrow indicates the possibility that negative health outcomes influence policy; this feedback is less likely to occur in the case of marginalized diseases

1976; Piesman et al. 1985; Gürtler et al. 1998a, 2005; Alroy et al. 2015; Cardinal et al. 2018; Fernández et al. 2019a). In a peri-urban community of Arequipa (Peru), child infection was instead associated with peridomestic infection in *T. infestans* (Levy et al. 2007). In rural villages of northwestern Argentina and northeast Brazil, human and vector infections were strongly and positively associated with the household presence and number of infected dogs (Cardinal et al. 2014; Gürtler et al. 1998a,b, 2005; Mott et al. 1978b).

In theory, the circulation of *T. cruzi* among multiple host species differing in reservoir competence might favor pathogen persistence (maintenance) or high pathogen abundance (amplification) or reduce both of them (the dilution effect) (Begon 2008). The empirical relations described above were embodied in a mathematical model of domestic transmission mediated by *T. infestans*, which accounted for host-species effects and seasonality (Cohen and Gürtler 2001). Having two or more *T. cruzi*-infected dogs disproportionately increased the prevalence of vector and human infection. Dogs acquired the infection within a few months of exposure, and 90–100% of dogs were infected by 3 years of age (Gürtler et al. 1996, 2007a). Although refractory to *T. cruzi* infection, the indoor occurrence of one or two nesting chickens boosted domestic bug populations beyond the constraints set by human and dog numbers and ultimately contributed to larger infected-bug abundances and human infection through frequent host shifts (Gürtler et al. 1998b) (see Sect. 2.5). Other model specifications reached similar conclusions: increasing the number of dogs would amplify the intensity of domestic transmission (Fabrizio et al. 2016;

Flores-Ferrer et al. 2019; Nouvellet et al. 2015; Peterson et al. 2015; Spagnuolo et al. 2012). The net effects of adding transmission non-competent hosts (chickens) on bug and host infection may vary with the precise details on the relative number and location of chickens, humans, and triatomine species involved and thus cannot be generalized to all ecological settings. The key finding is that chickens and selected domestic animals increase the equilibrium vector population size across triatomine species (e.g., Minter 1976; Dumonteil et al. 2018) and ultimately increase human-vector contact rates and exposure.

4 Social Determinants of Domestic Transmission

The social determinants of health (SDHs) condition both disease distribution and the ways they are handled (Manderson et al. 2009). Although the links between social factors and health outcomes have been widely recognized since the 1990s, the SDHs are often disregarded in biomedical research related to disease control because they fall outside the scope of traditional healthcare systems (Bizimana et al. 2015; Manderson et al. 2009). To address this issue, the World Health Organization has developed a conceptual framework to act upon the SDHs (Solar and Irwin 2010). This framework is based on the concept that “the social position of individuals and population groups is the main determinant of health inequalities within a community” by determining differential exposures to health-adverse conditions among individuals, differential consequences resulting from exposure (socioeconomic or health outcomes), and/or differential capabilities to recover (Solar and Irwin 2010).

The SDHs of Chagas disease include interrelated socioeconomic and demographic factors such as ethnicity, gender, occupation, educational level, and income, i.e., structural determinants (Ehrenberg and Ault 2005; Hotez et al. 2008; Aagaard-Hansen and Claire 2010; Solar and Irwin 2010). These determinants affect other factors more directly associated with disease exposure and outcome (i.e., intermediary determinants), such as household and dwelling characteristics.

4.1 Socioeconomic Factors

The social stratification of individuals and demographic groups results from, and also perpetuates, socioeconomic inequalities (Pluciński et al. 2013), leading some people to live in a state of relative or absolute poverty. Understanding poverty as a dynamic and multidimensional process (as opposed to a lack of resources) requires introducing the concept of social vulnerability, which considers the “defenselessness, insecurity, and exposure to risks, shocks and stress” experienced by households (Chambers 1989). The notion of social vulnerability summarizes the multiple, interrelated structural and intermediary determinants associated with the

socioeconomic position (SEP) of individuals and groups in a population. In the context of low- and middle-income countries, socioeconomic inequalities were represented using surrogate indicators such as educational attainment and household ownership of assets (Houweling et al. 2016). These indicators may only partially capture the full complexity of poverty. In particular, Chagas disease presents a disproportionately high disease burden on indigenous communities and poor rural peasants across Latin America (Hotez et al. 2008; Hotez 2014; Gürtler 2009). Although poverty has long been acknowledged as the main driver of Chagas disease risk (Ault 2007; Guhl et al. 2007; Briceño-León and Méndez Galván 2007; Gürtler 2009), evidence of the effects of socioeconomic inequalities is limited compared to other NTDs (Houweling et al. 2016; Fernández et al. 2019a).

The socioeconomic position of individuals and households is associated with other structural SDHs such as educational level, ethnicity, and income, which in turn will determine several intermediary SDHs associated with vector occurrence or invasion of human habitations, human exposure, and the resources required to deal with the consequences of vector exposure. However, finding appropriate measures of household SEP in low- and middle-income countries and in contexts of structural poverty is not trivial. Traditional income-based indices may fail to capture the full range of heterogeneity across household socioeconomic status (Booyesen et al. 2008; Howe et al. 2012), particularly in communities where household monetary income is principally dependent on the scarce jobs available and on welfare support, as in many endemic areas for Chagas disease.

As an alternative, several studies have explored the effects of SEP-related intermediary and structural SDHs on house infestation. Most of them focused on housing quality and construction materials because of their association with refuge availability rather than as a measure of SEP (Levy et al. 2006; Gurevitz et al. 2011; Dumonteil et al. 2013; Bustamante et al. 2014; Gaspe et al. 2015). Other studies investigated the effects of other surrogates of SEP on house infestation with *T. infestans* and the occurrence of infected domestic vectors, sometimes using overcrowding and/or ownership of livestock (goat-equivalent index) as surrogate indices of household wealth (Gaspe et al. 2015; Cardinal et al. 2018). Overcrowding (i.e., human density in sleeping quarters) incorporates both household size and number of rooms and was closely and positively associated with domestic infestation and bug abundance (Gaspe et al. 2015). Overcrowding is expected to facilitate host finding and blood-feeding success on humans and most likely underlies the positive relation between the number of human occupants and domestic infestation with triatomine bugs (Marsden et al. 1982; Piesman et al. 1983; Levy et al. 2006; Campbell-Lendrum and Woodruff 2007; Provecho et al. 2017; Cardinal et al. 2018). The goat-equivalent index was weakly and inversely associated with house infestation with *T. infestans* and the occurrence of infected vectors in the Argentine Chaco (Gaspe et al. 2015; Cardinal et al. 2018); although it captured part of the variability between households and demographic groups, the effect was not statistically significant. Another study that included SEP as a risk factor for house infestation with *T. dimidiata* in Guatemala found a moderate association between house infestation and two summary indices representing household assets (cell phone and livestock)

and access to electricity (Bustamante et al. 2014). For intrusive species such as *T. dimidiata*, artificial light in the house or in nearby streets was positively associated with house infestation (Pacheco-Tucuch et al. 2012; Dumonteil et al. 2013).

Educational level has also been considered a surrogate of SEP in studies of house infestation in Yucatan (Dumonteil et al. 2013) and in the Argentine Chaco (Gaspé et al. 2015), where it showed a negative and significant association with domestic infestation. A direct causal pathway from increasing household educational levels to decreasing infestation may be related to access to information and receptivity to health education messages, which may translate into healthier practices (Solar and Irwin 2010). For example, education levels correlated directly with the severity of Chagas disease cardiomyopathy (Viotti et al. 2009). However, educational level (as determined by the duration of formal instruction) does not specify its quality nor health education through informal channels (Gaspé et al. 2015) and most likely reflects socioeconomic inequalities between households.

The association between human infection with *T. cruzi* and selected sociodemographic factors in rural endemic areas has been a recurrent focus of interest (e.g., Gürtler et al. 1998a, b, 2005; Levy et al. 2007; Samuels et al. 2013; Alroy et al. 2015; Cardinal et al. 2018). However, these studies did not address the combined effects of ecological and social variables due to limited data availability. While human infection increased with infected-bug abundance and the household presence or number of domestic dogs (see Sect. 3.5), a less consistent association was found with house construction quality (i.e., thatched roofs and cracks in the walls): some studies reported an inverse relation between infection and selected aspects of housing quality (Mott et al. 1978a; Gürtler et al. 1998a, b, 2005; Samuels et al. 2013), whereas others did not (Levy et al. 2007; Alroy et al. 2015).

The multiple SDHs related to poverty (e.g., poor-quality housing, household overcrowding, and low educational level) may be summarized into a social vulnerability index by means of multiple correspondence analysis (Fernández et al. 2019a). The concept of social vulnerability may be taken as an *ex ante* risk that a household will fall below the poverty line or, if already poor, will remain in poverty (Chaudhuri et al. 2002). When considered as a SDH, social vulnerability refers to a predisposition of certain individuals or groups to acquire the disease(s) in question, and their capacity to respond and access the healthcare system (Hagenlocher and Castro 2015; Bizimana et al. 2015). In creole and indigenous households in the Argentine Chaco, the social vulnerability index was positively associated with house infestation and the abundance of *T. cruzi*-infected domestic triatomines and was negatively correlated with the asset index and domestic insecticide use (Fernández et al. 2019a). This analysis clearly reveals the tight links between triatomine exposure and resource constraints, poor housing quality (suitable habitats), householders' prevention practices, and sociodemographic factors that reflect and perpetuate poverty. Most importantly, the social vulnerability index was positively associated with human infection after adjusting for other relevant demographic and ecological factors (Fernández et al. 2019b).

Access to health services, an important determinant related to SEP, also depends on health and infrastructure-related policies (Solar and Irwin 2010). Access to health services includes the availability of healthcare facilities and personnel and the distance and transportation means available to the household. In general, evidence of the association between socioeconomic status and access to health services is scattered and seems to be context-dependent (Raso et al. 2005; Fürst et al. 2009). Other barriers to healthcare access in endemic rural communities include alleged discriminatory behaviors within the health system, especially of indigenous and other vulnerable groups (Dell’Arciprete et al. 2014; Brierley et al. 2014). In the Argentine Chaco, domestic infestation was significantly lower in houses with greater access to health services, possibly reflecting the aggregation of non-infested, new houses built around healthcare posts or their improved access to insecticides or capacity to demand vector control actions (Fernández et al. 2019a). Access to healthcare and other services were one of the main reasons for household mobility within rural communities and relocation in the periphery of the local town (Sect. 4.3).

4.2 Ethnicity

The intersection between SEP and ethnicity can further increase the inequalities observed in Chagas disease endemic areas, as explained by the intersectional paradigm (Hankivsky and Christoffersen 2008). Multiple indigenous groups live in Chagas disease endemic areas (Hotez et al., 2008). In the Gran Chaco region, the seroprevalence of *T. cruzi* in indigenous peoples tended to exceed that of creole residents (Basombrio et al. 1999; Taranto et al. 2003; Biancardi et al. 2003; Diosque et al. 2004; Alonso et al. 2009; Sosa-Estani et al. 2009; Moretti et al. 2010; Lucero et al. 2016; Cardinal et al. 2018). House infestation rates with *T. infestans* were higher in indigenous households, consistent with their more precarious living conditions (Gurevitz et al. 2011; Gaspé et al. 2015, 2018; Provecho et al. 2017) and greater social vulnerability (Fernández et al. 2019a). Their dogs and cats also displayed greater infection prevalence than those owned by creoles (Cardinal et al. 2014). However, the statistical effects of ethnic background ceased to be significant when other ecological and socioeconomic variables more closely related to house infestation or domestic triatomine abundance were incorporated to these multimodel-based analyses (Gurevitz et al. 2011). The effects of ethnicity on human infection with *T. cruzi* may be more complex than anticipated: while a twofold greater risk occurred among indigenous people after adjusting for social vulnerability and other factors in a section of Pampa del Indio (Fernández et al. 2019b), no effects were observed in another rural section including a majority of creole households (Cardinal et al. 2018). Cultural factors associated with ethnic background (Arrom-Suhurt et al. 2018) likely affected human exposure to triatomines.

4.3 Human Migration and Mobility

Human migration and mobility can affect domestic transmission patterns by facilitating vector dispersal and modifying exposure to the vector and by introducing *T. cruzi*-infected people and nonhuman reservoir hosts. Migration from endemic regions to non-endemic countries (driven mostly by economic/labor reasons) expanded Chagas disease to Europe and non-endemic areas in North America, Japan, and Australia (Schmunis and Yadon 2010; Lee et al. 2013). There, vertical transmission became the main transmission route (Sicuri et al. 2011; Howard et al. 2014), followed by transmission via blood transfusion and organ transplantation before the implementation of prevention measures (Girolamo et al. 2011). The SEP of migrants in the receiving country and their access to health services created a new set of challenges for case detection and treatment (Ventura-Garcia et al. 2013). The same argument holds for migration from endemic rural areas to non-endemic areas within Latin America.

The steady rural-to-urban migration recorded during the twentieth century and projected for future decades, combined with increasing travel and transportation of goods from rural to peri-urban or urban areas, provides multiple routes of entry of triatomine bugs into habitats wrongly assumed not to be at risk of infestation. Consequently, several species of triatomines (including *T. infestans*, *T. dimidiata*, *Triatoma pallidipennis*, and *Mepraia spinolai*) colonized peri-urban and urban habitats and even invaded the top stories of city buildings through flight dispersal (Vallvé et al. 1996; Albarracin-Veizaga et al. 1999; Cattán et al. 2002; Ramsey et al. 2005; Levy et al. 2006; Guzman-Tapia et al. 2007; Medrano-Mercado et al. 2008; Lima et al. 2012; Gaspe et al. 2020). Peri-urban areas, defined as “the areas where the urban core intermingles with adjacent ‘non-urban’ systems” (MacGregor-Fors 2011), provide a transition between urban and rural areas. In Latin America, peri-urban areas frequently include precarious settlements where new migrants usually first settle, occupying vacant land with low land-tenure security (Levy et al. 2014). Therefore, migration and settlement patterns may represent relevant risk factors for house infestation and transmission of *T. cruzi* (Bayer et al. 2009; Delgado et al. 2013; Levy et al. 2014). The combination of substandard housing quality and proximity between houses facilitates triatomine invasion (Levy et al. 2006).

Rural communities in the Argentine Chaco displayed significant rates of rural-to-urban migration, internal mobility (i.e., moving within the study area: local movers), and return of migrants from urban areas (Fernández et al. 2019a). These migration and mobility patterns differed between ethnic groups: creoles displayed the traditional rural-to-urban movement (Briceño-León 2009), whereas indigenous (Qom) migration rates equaled internal mobility rates, with in-migration almost fully compensating out-migration. Qom mobility patterns are rooted in socioeconomic and cultural factors: nomadic traditions (Maidana 2011), formation of new families, household mobility to gain increased access to basic services (e.g., better water sources and school), and cultural reasons (decease of the head of family). Local mobility implied elevated house turnover rates causing substantial negative effects on extant house infestations (Gaspe et al. 2015, 2018) and possibly created

additional heterogeneities in human-vector contact rates (Stoddard et al. 2009). Local movers were likely exposed to lower, more variable infestations over time and greater chances of occupying an infested house than non-movers (Fernández et al., 2019a).

Human mobility in interaction with vector exposure created complex patterns in the seroprevalence rates of children from stable households (non-movers) and among movers (Fernández et al. 2019b). Among non-mover children, infection prevalence was sixfold greater when domestic premises were infested (as expected from prolonged vector exposure), whereas no significant association between child infection and domestic infestation occurred among movers (Fernández et al. 2019b). In a peri-urban area of Arequipa, domestic infestation was positively associated with land-tenure security (i.e., more established households, rather than more recent immigrants), suggesting that although land-tenure security may pave the way to improved house quality, it may also provide a more stable environment for triatomine establishment (Levy et al. 2014). Further research is needed to disentangle the effects of internal mobility on triatomine and human exposure dynamics and gauge the relative magnitude of these effects in endemic communities with different socio-economic and demographic profiles.

4.4 Interactions Between Social and Ecological Factors

Understanding the domestic transmission of *T. cruzi* requires a better understanding of the interactions between ecological and social factors such as SEP, ethnicity, and household mobility. In rural communities of the Argentine Chaco, the intersection between ethnicity and SEP further combined with human mobility patterns: movers had higher social vulnerability than non-movers both within indigenous and creole households (Fernández et al. 2019a). The relative odds of human infection varied significantly with the interaction between social vulnerability index and infected-vector abundance: infected-vector abundance exerted lower effects (on a per capita basis) in households with higher social vulnerability (Fernández et al. 2019b). This unexpected effect may be explained by several nonexclusive reasons: (i) social vulnerability may also indicate past exposure to triatomines; (ii) households with higher social vulnerability had greater local mobility, suggesting putative vector exposures elsewhere; and (iii) more frequent human-triatomine contact given the greater overcrowding in households with higher social vulnerability.

5 Scaling Up from Household- to Population-Level Transmission

Although the domestic transmission of *T. cruzi* is clustered at a household level (Mott et al. 1976; Gürtler et al. 1998a, b; Levy et al. 2007; Cardinal et al. 2014,

2018; Fernández et al. 2019b), the combination of human mobility, spatial distribution of houses, and community-level variables (e.g., insecticide spraying or housing improvement efforts) may generate new properties at higher spatial scales. By scaling up from household-level dynamics to the population level, we may gain insight into the ecological and social factors associated with human infection and the impact of community-based vector control actions. The joint analysis of the spatial distribution of human and vector infection can shed light into the processes and factors associated with vector-borne transmission of *T. cruzi*. By integrating the spatial component of infection with household-level and individual-based risk factor analysis, we may identify transmission hotspots, create risk maps of *T. cruzi* infection, and stratify the affected areas for targeted control (Fortin and Dale 2005; Wiegand and Moloney 2014).

By contrast to vector-related research, the spatial component of human *T. cruzi* infection has rarely been investigated (Levy et al. 2007, 2009; Delgado et al. 2011; Fernández et al. 2019b). As stated by Houweling et al. (2016), “spatial clustering of infection because of geographic conditions, among other causes, is typical for most NTDs.” Spatial clustering may also be context-specific and depend on the intersection between social and ecological factors. The spatial aggregation of house infestation (e.g., Cecere et al. 2004; Gaspe et al. 2015) and of human cases of *T. cruzi* infection across settings and scales indicates that spatial heterogeneity is the rule rather than the exception and that transmission is not restricted to the household. The underlying community-level processes possibly emerge from a combination of active and passive vector dispersal (Levy et al. 2006; Gurevitz et al. 2011; Gaspe et al. 2013, 2015; Provecho et al. 2017), the aggregation of more vulnerable households, and the effects of human mobility (Gaspe et al. 2015, 2018; Fernández et al. 2019a). These in turn can be affected by social networks and public policies. Integrating the ecological and social determinants of human infection with the spatial component is key to the design of more cost-effective vector control strategies in resource-constrained areas to identify higher-priority areas for targeted interventions oriented to suppress house (re)infestations, treat infected children, and thus reduce the current and future burden of disease.

Acknowledgments We are grateful to Carla Cecere, Sol Gaspe, Gustavo Enriquez, Yael Provecho, Paula Sartor, and Natalia Macchiaverna for helpful discussions. This work was supported by the University of Buenos Aires (UBACYT 20020130100843BA), PICT 2014-2661 and PICT 2015-2921.

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