



Enhanced Attraction of Arthropod Vectors to Infected Vertebrates: A Review of Empirical Evidence

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A large diversity of parasites manipulates their hosts in various ways to complete their own life cycle. Enhancing the attractiveness of their host to vectors has been suggested as a strategy allowing vector-borne parasites to increase their transmission. Indeed, a higher attraction of hematophagous, arthropod vectors to infected vertebrates compared to uninfected individuals has been found in many systems (e.g., *Trypanosoma*-tsetse flies, *Leishmania*-sand flies, *Borrelia*-ticks) but was most often verified in the *Plasmodium*-mosquitoes model. However, a number of studies found no difference in attractiveness, or a higher attractiveness of uninfected hosts. In this review, we present studies reporting a comparison of the attractiveness and/or the biting rate of infected and uninfected vertebrates. We then discuss several biological factors and experimental design aspects that can explain discrepancies between studies. Finally, we stress the importance of investigating the mechanisms of parasite-induced increased attractiveness of infected hosts to conclude that such observations are cases of adaptive manipulation.

Keywords: attractiveness, extended phenotype, hematophagous arthropods, host-choice, host-seeking, manipulation, vector-borne parasites

INTRODUCTION

Host manipulation by parasites has been fascinating parasitologists for decades (Thomas et al., 2005), especially when this manipulation results in dramatic changes in host's physiology (Cordaux et al., 2011; Kageyama et al., 2012; Fayard et al., 2020), morphology (Bakker et al., 1997; Yanoviak et al., 2008; Fayard et al., 2020) or behavior (Berdoy et al., 2000; Thomas et al., 2002; Weinersmith, 2019; Fayard et al., 2020). This host exploitation strategy, described in many phylogenetically distant host-parasite systems, usually involves phenotypic changes in the infected host (extended phenotype, Dawkins, 1982). These alterations can be mediated by direct or indirect mechanisms (Thomas et al., 2005). Parasites can produce, store and release active manipulation factors that act directly on host tissues such as the nervous system or muscles. These manipulative factors are part of a complex mixture of molecules called the secretome (Adamo, 2013; Biron and Loxdale, 2013; Berger and Aubin-Horth, 2020). On the other hand, the mere physical presence of parasites in particular tissues or simply the pathological by-products of infection can influence the development and/or the metabolism of the host, secondarily leading to an alteration of its phenotype (Dingemanse et al., 2009; Thomas et al., 2012).

Vector-borne parasites have evolved different angles of attack to increase their own transmission by manipulating their vectors and hosts (Lefèvre and Thomas, 2008). Indeed, infected vectors

show alterations in host-seeking and feeding behaviors, fecundity and longevity [reviewed in Hurd (2003), Cator et al. (2012), Murdock et al. (2017), Stanczyk et al. (2017)], microhabitat preference (Fialho and Schall, 1995) and selection of host species (Vantaux et al., 2018 but see Nguyen et al., 2017; Vogels et al., 2017), that all seem beneficial for the transmission of the parasites they harbor. For example, impaired ingestion forcing the vector to bite several times to achieve a complete blood-meal has been reported in *Trypanosoma*-infected tsetse flies and kissing bugs, *Leishmania*-infected sand-flies, *Plasmodium*-infected mosquitoes and plagued fleas [reviewed in Hurd (2003)]. Although this example can be considered as a simple pathological consequence of the infection with coincidental benefit for transmission, the convergent appearance of this phenomenon was hypothesized to reflect adaptive manipulation (Poulin, 1995).

In addition, parasites seem able to make their vertebrate hosts more attractive to their vectors. From this point of view, the vectors can be considered as “exploited”, because their host-seeking behavior is indirectly influenced by an alteration of the infected vertebrate’s phenotype. Although increased attractiveness of infected hosts has been reported in various host/parasite systems, many studies have obtained conflicting results. Here, we first propose a review of the current knowledge on this topic by gathering all the studies that have empirically investigated the impact of infection of vertebrate hosts on their attractiveness to arthropod vectors. We also take stock of current knowledge on the mechanisms potentially involved in attraction bias. Then, based on a review of the materials and methods used to study attraction bias, we seek to identify crucial aspects of the experimental designs that could explain the contradictory results frequently observed.

CURRENT KNOWLEDGE ON THE ATTRACTION OF ARTHROPOD VECTORS TO INFECTED VERTEBRATES

Integration of Vector Feeding Bias in Epidemiological Models

For over a century, the epidemiology of vector-borne diseases was addressed using mathematical models describing the life cycle of pathogens in vertebrate and invertebrate (vector) hosts. Although the early models included several strong assumptions, which greatly simplified the complex host-vector interactions (Ross, 1916; Macdonald, 1956, 1957; Bailey, 1975), they highlighted the impact of different host and vector life-cycle parameters on parasite transmission and, in particular, they pointed out that the vector’s biting rate could have major consequences on transmission dynamics. Then, epidemiological models became more and more complex by integrating new parameters such as vector feeding bias. Whereas early models assumed that vectors chose hosts and fed on them randomly, and therefore independently of the absence or presence of infection, empirical data acquired in the early 1980s have overturned this paradigm. It was observed that mosquitoes preferentially fed on malaria-infected rather than uninfected mice (Day and Edman, 1983;

Day et al., 1983). Based on this observation, Kingsolver was the first to develop and analyze a model for the dynamics of parasite transmission that incorporates nonrandom feeding behavior by the vector (Kingsolver, 1987). He demonstrated that increasing the preference of vectors for infected hosts leads to an easier maintenance of a stable infection, compared to the model where vectors feed on their host in a random manner. Subsequent studies confirmed this result and showed that the preference of vectors for infected hosts can strongly reinforce the transmission of the parasite at the beginning of the epidemic (McElhany et al., 1995; Hosack et al., 2008; Sisterson, 2008; Chamchod and Britton, 2011; Zeilinger and Daugherty, 2014; Gandon, 2018). Parasites that are able to manipulate their vertebrate hosts to make them more attractive to vectors should be therefore favored by natural selection. However, an extreme preference of vectors for infected hosts may also limit or stop the transmission of parasites (Kingsolver, 1987; McElhany et al., 1995; Sisterson, 2008; Zeilinger and Daugherty, 2014; Gandon, 2018). Indeed, when levels of host infection in a population are very high, vector feeding bias results in most of the bites occurring on already infected hosts. Natural selection should then favor parasites that induce either an intermediate level of attractiveness or a conditional change in the behavior of the vector depending on its own infection status (see Gandon, 2018).

Empirical Evidence of Parasite Manipulation of Host Attractiveness

We gathered the studies that investigated the manipulation of host attractiveness to vector-borne parasites, by searching Google Scholar and Web of Science databases with combinations of the terms “vector” and “parasite” or “virus” or “bacteria” and “attraction” or “attractiveness” or “choice” or “host selection” or “olfactometer” or “preference.” All studies that report an observational or experimental comparison of the numbers of arthropod vectors that were attracted to and/or bit infected and uninfected vertebrates were selected. We also included experiments using only the odor of the vertebrates. These studies are summarized in **Table 1** (Culicidae) and **Table 2** (other invertebrate vectors). The majority of studies focused on Culicidae vectors and *Plasmodium* infection, finding in most cases, but not always, that mosquitoes are more attracted to *Plasmodium*-infected hosts (12/18; **Table 1, Figure 1**).

Only two studies looked for a biased attractiveness of hosts infected with filarial worms and found none (Burkot et al., 1989; Kruppa and Burchard, 1999). More tsetse flies (*Glossina pallidipes*) bit the Orma Boran oxen infected with *Trypanosoma congolense*, but not those infected by *Trypanosoma vivax* (Baylis and Nambiro, 1993; Baylis and Mbwabi, 1995), and only hybrids of the *Triatoma dimidiata* complex preferred *Trypanosoma cruzi*-infected mice over uninfected ones (Ramirez-Sierra and Dumonteil, 2016). *Leishmania infantum* made their hamster hosts more attractive to *Lutzomyia longipalpis* (O’Shea et al., 2002; Nevatte et al., 2017), but *Leishmania braziliensis* did not enhance attractiveness of mice for *Nyssomyia neivai* (da Rocha Silva et al., 2019). The probability that a bat fly chose a host was negatively

TABLE 1 | Summary of studies comparing attractiveness of infected and uninfected hosts to mosquitoes.

Host	Vector	Parasite	Most attractive hosts	Method	Compared treatments	Infection	Setup	Vector infection status	Defensive behavior, activity	Comment	Reference	Citations
<i>Rana clamitans</i>	<i>Culex pipiens</i>	<i>Hepatozoon clamatae</i>	Infected	Comparison of biting rates	Infected vs uninfected individuals	Natural	Lab	Uninfected	Possible		Ferguson et al., 2013	8
			None	Comparison of biting rates	Infected vs uninfected individuals	Experimental						
	Infected		Choice, biting	Infected vs uninfected individuals	Natural							
	None		Choice, probing	Infected vs uninfected individuals	Experimental							
<i>Thamnomphis sirtalis</i>	<i>Culex pipiens</i>	<i>Hepatozoon sipedon</i>	Infected	Choice, biting	Infected vs uninfected individuals	Natural						
<i>Homo sapiens</i>	<i>Anopheles darlingi</i>	<i>Plasmodium vivax</i>	Infected	Comparison of attraction rates in olfactometer (individuals)	During infection vs after anti-parasite treatment	Natural	Lab	Uninfected	Impossible	Only gametocyte carriers were more attractive	Batista et al., 2014	25
			Infected	Comparison of attraction rates in olfactometer (individuals)	Infected vs uninfected individuals							
<i>Homo sapiens</i>	<i>Anopheles farauti</i>	<i>Plasmodium spp.</i>	None	Comparison of biting rates	Infected vs uninfected individuals	Natural	Wild	Uninfected	Possible but unlikely (sleeping)		Burkot et al., 1989	23
	<i>Anopheles punctulatus</i>	<i>Plasmodium spp.</i>	Uninfected	Choice, biting	Infected vs uninfected individuals							
			<i>Wuchereria bancrofti</i>	None	Choice, biting	Infected vs uninfected individuals						
<i>Homo sapiens</i>	<i>Anopheles coluzzii</i>	<i>Plasmodium falciparum</i>	None	Comparison of attraction rates in olfactometer (skin odor)	Infected vs uninfected individuals	Experimental	Lab	Uninfected	Impossible	Effect was present in one of two experimental blocks	de Boer et al., 2017	15
			Uninfected		Before infection vs during infection							
			Uninfected		During infection vs after anti-parasite treatment							
			None		Infected vs uninfected individuals							
			None		Before infection vs during infection							
			None		During infection vs after anti-parasite treatment							
<i>Homo sapiens</i>	<i>Anopheles gambiae</i>	<i>Plasmodium falciparum</i>	Infected	Comparison of attraction rates in olfactometer (individuals)	During infection vs after anti-parasite treatment	Natural	Lab	Uninfected	Impossible	Only gametocytes carriers were more attractive	Lacroix et al., 2005	171

(Continued)

TABLE 1 | Continued

Host	Vector	Parasite	Most attractive hosts	Method	Compared treatments	Infection	Setup	Vector infection status	Defensive behavior, activity	Comment	Reference	Citations
			Infected	Dual-choice olfactometer (individuals)	Infected vs uninfected individuals							
<i>Homo sapiens</i>	<i>Anopheles gambiae</i>	<i>Plasmodium falciparum</i>	None	Dual-choice olfactometer (individuals)	NA	Natural	Lab	Unknown	Impossible	Only two men compared, based on their symptoms	Mukabana et al., 2007	5
<i>Homo sapiens</i>	<i>Anopheles gambiae</i>	<i>Plasmodium falciparum</i>	Infected	Comparison of attraction rates in olfactometer (individuals)	During infection vs after anti-parasite treatment	Natural	Lab	Uninfected	Impossible	Only microscopic gametocyte carriers were more attractive	Busula et al., 2017a	19
			Infected	Comparison of attraction rates in olfactometer (individuals)	Infected vs uninfected individuals							
<i>Homo sapiens</i>	<i>Anopheles gambiae</i>	<i>Plasmodium falciparum</i>	Infected	Dual-choice olfactometer (skin odor)	During infection vs after anti-parasite treatment	Natural	Lab	Uninfected	Impossible	Both gametocytes carriers and asexual stages carriers were more attractive	Robinson et al., 2018	25
<i>Mus musculus</i>	<i>Aedes aegypti</i>	<i>Plasmodium yoelii</i>	Infected	Comparison of attraction rates	Before infection vs during infection	Experimental	Lab	Uninfected	Possible and monitored: infected less active		Coleman et al., 1988	9
			None	Comparison of biting rates	Infected vs uninfected individuals							
		<i>Leishmania mexicana amazonensis</i>	None	Comparison of attraction rates	Before infection vs during infection							
			None	Comparison of biting rates	Infected vs uninfected individuals							
		<i>Plasmodium yoelii</i> and <i>Leishmania mexicana amazonensis</i>	Infected	Comparison of attraction rates	Before infection vs during infection					Only during peak of infection were the hosts more attractive		
			Infected	Comparison of biting rates	Infected vs uninfected individuals							

(Continued)

TABLE 1 | Continued

Host	Vector	Parasite	Most attractive hosts	Method	Compared treatments	Infection	Setup	Vector infection status	Defensive behavior, activity	Comment	Reference	Citations
<i>Mus musculus</i>	<i>Aedes aegypti</i>	<i>Plasmodium bergeri</i>	Infected	Comparison of biting rates	Infected vs uninfected individuals	Experimental	Lab	Uninfected	Possible and monitored: infected less defensive	Only just after the acute phase were the hosts more attractive; was linked with defensive behavior.	Day et al., 1983	48
		<i>Plasmodium chabaudi</i>	Infected	Choice, biting								
		<i>Plasmodium chabaudi</i>	Infected	Comparison of biting rates								
		<i>Plasmodium chabaudi</i>	Infected	Choice, biting								
<i>Mus musculus</i>	<i>Anopheles stephensi</i>	<i>Plasmodium chabaudi</i>	Infected	Dual-choice olfactometer (individuals)	Infected vs uninfected individuals	Experimental	Lab	Uninfected	Impossible	The hosts were more attractive right after the acute phase, when gametocytes were still present.	de Moraes et al., 2014	61
			Infected	Dual-choice olfactometer (volatiles)								
<i>Mus musculus</i>	<i>Anopheles stephensi</i>	<i>Plasmodium chabaudi</i>	Infected	Comparison of biting rates	Infected vs uninfected individuals	Experimental	Lab	Uninfected	Impossible		Ferguson et al., 2003	35
<i>Serinus canaria</i>	<i>Culex pipiens</i>	<i>Plasmodium relictum</i>	Infected	Comparison of biting rates	Before infection vs during infection	Experimental	Lab	Uninfected	Impossible	More attractive only during chronic stage	Cornet et al., 2013b	63
			Infected	Choice, biting	Infected vs uninfected individuals							
<i>Serinus canaria</i>	<i>Culex pipiens</i>	<i>Plasmodium relictum</i>	Infected	Choice, biting	Infected vs uninfected individuals	Experimental	Lab	Infected and uninfected	Impossible		Cornet et al., 2013a	29
<i>Gallus gallus domesticus</i>	<i>Aedes aegypti</i>	<i>Plasmodium gallinaceum</i>	Uninfected	Choice, biting	Infected vs uninfected individuals	Experimental	Lab	Uninfected	Impossible		Freier and Friedman, 1976	37
<i>Parus major</i>	<i>Culex pipiens</i>	<i>Plasmodium spp.</i>	Uninfected	Dual-choice olfactometer (individuals)	Infected vs uninfected individuals	Natural	Lab	Uninfected	Impossible		Lalubin et al., 2012	14

(Continued)

TABLE 1 | Continued

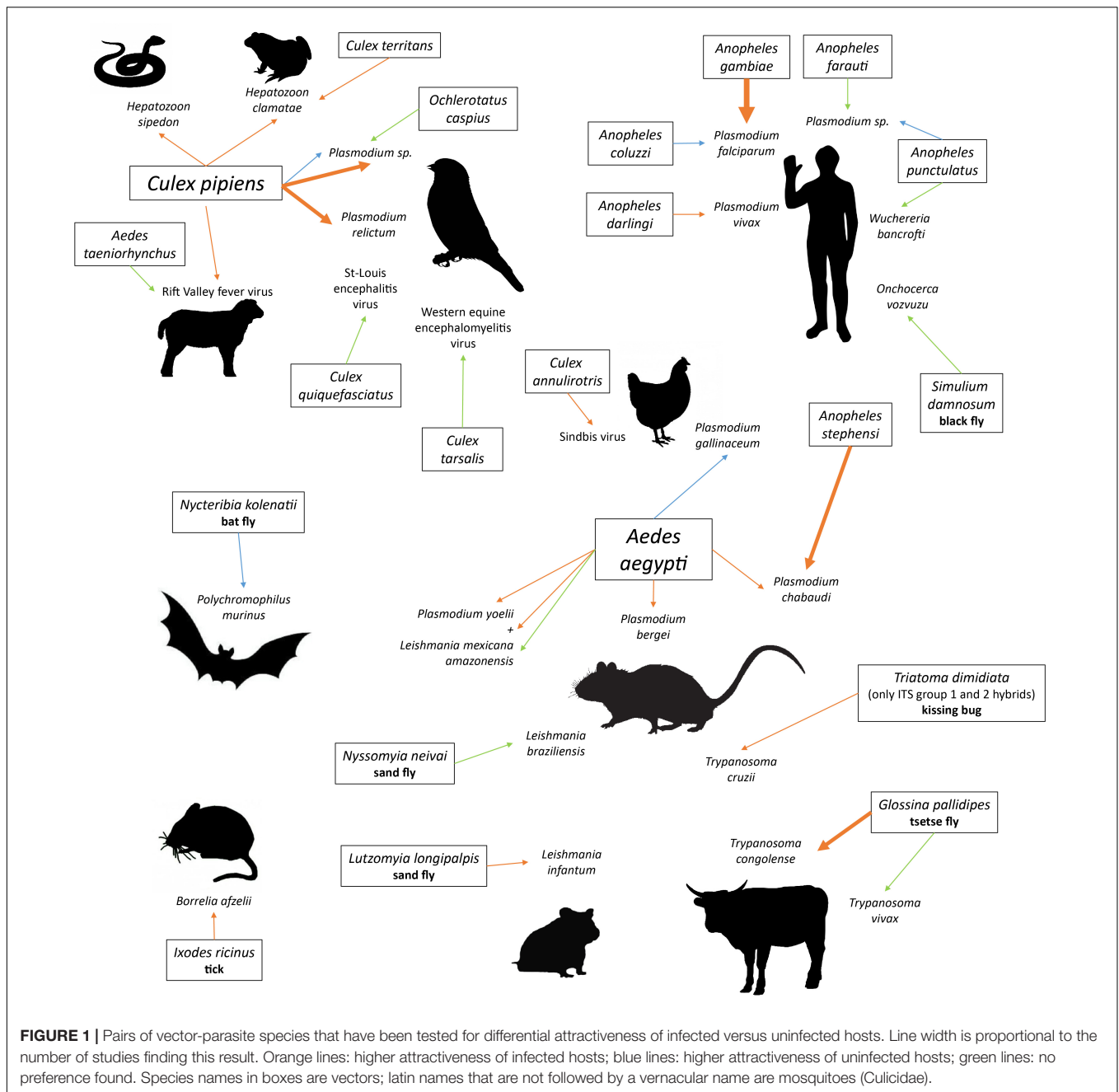
Host	Vector	Parasite	Most attractive hosts	Method	Compared treatments	Infection	Setup	Vector infection status	Defensive behavior, activity	Comment	Reference	Citations
<i>Coloeus monedula</i>	<i>Culex pipiens</i>	<i>Plasmodium spp.</i>	None	Comparison of biting rates	Infected vs uninfected individuals	Natural	Lab	Uninfected	Impossible		Gutiérrez-López et al., 2019	5
	<i>Ochlerotatus caspius</i>		None									
<i>Passer domesticus</i>	<i>Culex pipiens</i>	<i>Plasmodium spp.</i>	None		Infected vs uninfected individuals	Natural	Lab	Uninfected	Impossible		Díez-Fernández et al., 2020	0
	<i>Ochlerotatus caspius</i>		None									
<i>Passer domesticus</i>	<i>Culex pipiens</i>	<i>Plasmodium spp.</i>	Infected	Dual-choice olfactometer (headspace)	Infected vs uninfected individuals	Natural	Lab	Uninfected	Impossible		Díez-Fernández et al., 2020	0
			None	Dual-choice olfactometer (uropygial gland extract)								
<i>Passer domesticus</i>	<i>Culex pipiens</i>	<i>Plasmodium spp.</i>	Infected	Comparison of biting rates	During infection vs after anti-parasite treatment	Natural	Lab	Uninfected	Possible	The effect was correlated to the parasite density.	Yan et al., 2018	5
			None	Choice, biting	Infected vs uninfected individuals							
<i>Passer domesticus</i>	<i>Culex quinquefasciatus</i>	St. Louis encephalitis virus	None	Comparison of attraction rates in olfactometer (individuals)	Infected vs uninfected individuals	Experimental	Lab	Uninfected	Impossible		Scott et al., 1990	27
	<i>Culex tarsalis</i>	Western equine encephalomyelitis virus	None									
<i>Gallus gallus domesticus</i>	<i>Culex annulirostris</i>	Sindbis virus	Infected	NA	NA	Experimental	Wild	NA	NA		Mahon and Gibbs, 1982	25
			Infected	Choice, biting								
<i>Ovis aries</i>	<i>Culex pipiens</i>	Rift Valley fever virus	Infected	Choice, biting	Infected vs uninfected individuals	Experimental	Lab	Uninfected	Possible and monitored: infected less active		Turell et al., 1984	33
	<i>Aedes taeniorhynchus</i>		None									

Google Scholar and Web of Science databases were searched with combinations of the terms “vector” and “parasite” or “virus” or “bacteria” and “attraction” or “attractiveness” or “choice” or “host selection” or “olfactometer” or “preference.” The numbers of citations were retrieved from Web of Science on May 5th, 2020. The “infection” column refers to the way the infection was initiated; “Natural” means the vertebrate host was already harboring an infection when caught, while “Experimental” means the experimenters performed the inoculation in the lab.

TABLE 2 | Summary of studies comparing attractiveness of infected and uninfected hosts to non-mosquito vectors.

Host	Vector	Parasite	Most attractive hosts	Method	Infection	Setup	Vector infection status	Defensive behavior, activity	Comment	Reference	Citations	
Orma Boran oxen	<i>Glossina pallidipes</i>	<i>Trypanosoma congolense</i>	Infected	Comparison of biting rates	Natural	Wild	Unknown	Possible		Baylis and Nambiro, 1993	21	
			None	Choice, no biting								
Orma Boran oxen	<i>Glossina pallidipes</i>	<i>Trypanosoma congolense</i>	Infected	Comparison of biting rates	Natural	Wild	Unknown	Possible and monitored: did not differ	The effect did not depend on parasite density.	Baylis and Mbwabi, 1995	16	
			None									
<i>Mus musculus</i>	<i>Triatoma dimidiata</i> group 1	<i>Trypanosoma cruzi</i>	None	Dual-choice olfactometer	Experimental	Lab	Uninfected	Impossible		Ramirez-Sierra and Dumonteil, 2016	5	
			None									
			Infected									
<i>Homo sapiens</i>	<i>Simulium damnosum</i> complex	<i>Onchocerca volvulus</i>	None	Choice, biting	Natural	Wild	Unknown	Impossible		Kruppa and Burchard, 1999	5	
			Infected	Dual-choice olfactometer	Natural	Lab	Unknown	Impossible		van Duijvendijk <i>et al.</i> , 2016	4	
<i>Myodes glareolus</i>	<i>Ixodes ricinus</i>	<i>Borellia afzelii</i>	Infected	Dual-choice olfactometer	Natural	Lab	Unknown	Impossible				
			Infected	Choice, biting					Possible	Only males were more attractive.		
<i>Myotis daubentonii</i>	<i>Nycteribia kolenatii</i>	<i>Polychromophilus murinus</i>	Uninfected	Choice, biting	Natural	Lab	Unknown	Possible	The effect was correlated to the parasite density.	Witsenburg <i>et al.</i> , 2015	9	
<i>Mesocricetus auratus</i>	<i>Lutzomyia longipalpis</i>	<i>Leishmania infantum</i>	Infected	Dual-choice olfactometer	Experimental	Lab	Uninfected	Impossible		O'Shea <i>et al.</i> , 2002	34	
<i>Mesocricetus auratus</i>	<i>Lutzomyia longipalpis</i>	<i>Leishmania infantum</i>	Infected	Dual-choice olfactometer, choice between scents of individual before and during infection	Experimental	Lab	Uninfected	Impossible	The hosts were more attractive only during late stage of infection.	Nevatte <i>et al.</i> , 2017	4	
<i>Mus musculus</i>	<i>Nyssomyia neivai</i>	<i>Leishmania braziliensis</i>	None	Comparison of attraction rates in olfactometer	Experimental	Lab	Uninfected	Impossible		da Rocha Silva <i>et al.</i> , 2019	0	
			None	Choice, biting								

Google Scholar and Web of Science databases were searched with combinations of the terms "vector" and "parasite" or "virus" or "bacteria" and "attraction" or "attractiveness" or "choice" or "host selection" or "olfactometer" or "preference." The numbers of citations were retrieved from Web of Science on May 5th, 2020.



correlated with *Polychromophilus murinus* parasitaemia in the Daubenton bat (*Myotis daubentonii*) (Witsenburg et al., 2015). The only non-insect study that we found showed that male bank voles infected with the bacteria *Borrelia afzelli* harbored more ticks (van Duijvendijk et al., 2016). Finally, a few early studies investigated the attractiveness of virus-infected animals and found mitigated results (Mahon and Gibbs, 1982; Turell et al., 1984; Scott et al., 1990).

Mechanisms of Enhanced Attraction

Vectors of endoparasites infecting vertebrates are usually hematophagous arthropods, mostly insects and ticks. Insects

perceive olfactory molecules thanks to receptor neurons in sensilla, distributed on their antennae, maxillary palps and labia (Keil, 2012; Suh et al., 2014). Ticks sense volatile organic compounds (VOC) through a specific organ called Haller's organ located on their first pair of legs. Although not well known yet, it seems that chemoreceptors on Haller's organ are not similar to those on insects' sensilla (Carr et al., 2017). Molecules found to trigger responses in hematophagous arthropods mostly fall into the following categories: short chain carboxylic acids, aldehydes or low molecular weight nitrogenous compounds like ammonia (Syed, 2015). Indole and 1-octen-3-ol are often identified as attractant among the studied

insects, and carbon dioxide attracts all vectors (triatomines, cimicidae, ticks, tsetse flies, sand flies and mosquitoes; Syed, 2015). Carbon dioxide is also used in long-distance detection by host-seeking insects (Gillies, 1980). Mosquitoes can perceive very small variations of CO₂ concentration, like for instance *Aedes aegypti*, which has a detection threshold between 150 and 300 ppm and can perceive increments of 50 ppm (Grant et al., 1995). Cues used by vectors to select hosts are scattered in the air through the breath, the skin, and the excretions (Takken, 1991).

Recent studies have identified how VOC profiles differ between infected and uninfected hosts, and which compounds are involved in influencing attractiveness. Profiles of VOCs produced by humans and mice infected by *Plasmodium falciparum* and *Plasmodium chabaudi*, respectively, show they produce some compounds in higher quantities, while other compounds are suppressed in infected hosts (de Moraes et al., 2014; de Boer et al., 2017; Robinson et al., 2018). Some of these compounds (e.g., hexanoic acid, 2- and 3-methyl butanoic acid and tridecane in mice, heptanal, tetradecanoic acid, 3-methyl-1-butanol, and butan-1-amine in humans) have been shown to elicit a preference when added to the scent of a non-infected host (de Moraes et al., 2014; Robinson et al., 2018). Octanal, nonanal and decanal are among VOCs that showed significant variations between healthy dogs and dogs infected with *Leishmania infantum* (Magalhães-Junior et al., 2014), and were attractive to male sand fly vectors *Lutzomyia longipalpis* (Magalhães-Junior et al., 2019).

These attractive molecules can be produced by the infected host, by the parasite itself, or by the host microbiota. There is evidence that *Plasmodium* can synthesize terpenes, to which mosquitoes respond (Kelly et al., 2015), although they were not identified from infected mice or infected human skin and breath emissions (de Moraes et al., 2014; Berna et al., 2015; Robinson et al., 2018). Some malaria-associated VOCs are known to be produced by skin bacteria (de Moraes et al., 2014; de Boer et al., 2017). *Plasmodium* infection could cause a change in host microbial species composition, possibly mediated by immunological or endocrine systems (Busula et al., 2017b). Emami et al. (2017) have shown that a metabolite produced by *Plasmodium falciparum* ((E)-4-hydroxy-3-methyl-but-2-enyl pyrophosphate; HMBPP) induces red blood cells to produce molecules involved in mosquito attraction (CO₂, aldehydes, and monoterpenes). The mechanisms involved in these potential parasite-induced phenotypic alteration (Poulin, 1995) are yet not all identified and several unknowns remain to be discovered (Busula et al., 2017b; Joice Cordy, 2020).

EXPERIMENTAL DESIGNS AND CONFLICTING RESULTS

Although most of the investigated vector-borne parasite genera are featured in at least one study finding that infected hosts attract more vectors or are more often bitten than uninfected hosts (Figure 1), it is difficult to determine whether this is a widespread

phenomenon. One of the reasons for this is that the methods used to study vector attraction bias vary considerably from one study to another, making it impossible to draw an overall picture. In this second part, we have sought to identify aspects of experimental designs that may explain why, for the same parasite/vector pair, studies come to different conclusions.

Infection Stage and Parasite Density

A source of discrepancies between conclusions of studies might come from the parasite developmental stages in the timeframe of the experiments. Enhanced attractiveness of the infected vertebrate host should coincide with stages when the parasites are transmissible to vectors. This is confirmed by most studies checking for parasite developmental stages, which found that only *Plasmodium* gametocytes (sexual, transmissible stage) carriers were more attractive to *Anopheles* mosquitoes [Lacroix et al., 2005; Batista et al., 2014; de Moraes et al., 2014; Busula et al., 2017a, reviewed in Busula et al. (2017b), but see Robinson et al. (2018)]. Most studies finding a preference for the uninfected hosts did not verify whether the infected host exhibited transmissible stages (Freier and Friedman, 1976; Burkot et al., 1989; Lalubin et al., 2012). de Boer et al. (2017) did control but found no gametocytes in the tested individuals. The exception comes from Witsenburg et al. (2015) who found that bat flies that switched hosts ended up more often on the one with the lowest density of *Polychromophilus murinus* gametocytes, a malaria-like parasite. While attracting vectors when harboring transmissible stages seems like a selective advantage for parasites, it would bring no benefit during non-transmissible stages. Premature blood meals might even be deleterious, for example if they bring new parasites that may compete for resources, trigger a stronger immune response or kill their host before their own transmission.

Plasmodium infection dynamics in the blood is in general composed of two stages: the acute phase, a few days after infection, characterized by a peak in parasite density, followed by the chronic phase, with low parasite density (Garnham, 1966). Hosts harboring high parasite densities during the acute stage of *Plasmodium* infections were sometimes found to be less or equally attractive than uninfected hosts, and hosts became more attractive once the peak passed (Cornet et al., 2013b; de Moraes et al., 2014). Authors suggested that, as blood characteristics linked to immune response suppress infectivity (Mendis et al., 1987; Naotunne et al., 1993; Ramiro et al., 2011), it makes it useless for the parasite to attract vectors when the proportion of gametocytes relative to asexual stages is low, even if the absolute quantity of gametocytes may be higher than during other infection stages. In addition, the strong reduction in red blood cells counts following erythrocytic meronts rupture makes the blood less nutritious, and thus potentially less attractive for hematophagous arthropods. This hypothesis could be tested by examining the attraction of hematophagous species to individuals infected with parasites that they do not transmit. A recent study suggests that at least *Amblyomma* tick nymphs do not avoid birds infected with haemosporidian parasites (Fecchio et al., 2020). However, ectoparasites that are relatively less mobile, such as ticks, might

not be the best models to test this, as the cost of being too selective might be high, especially if the chances to encounter several potential hosts are low.

Conversely, Day et al. (1983) found that peak parasitaemia of *P. chabaudi* was associated with a peak of biting rate by *Aedes aegypti*, probably because infected mice exhibited fewer defensive behaviors due to illness. Similarly, *P. berghei*-infected mice were more bitten in the end of infection before mice died (but also right before the increase in parasitaemia), which can also be associated with the decrease in anti-mosquito behavior. Sickness behavior-linked reduction in anti-mosquito behavior could also explain Coleman et al.'s results (1988), who found that *Plasmodium yoelii* and *Leishmania mexicana amazonensis* co-infected mice were more bitten by *Aedes aegypti* than single- or un-infected mice, especially when the infection symptoms were the most severe.

Experimental Setup and the Importance of Controlling for Host Behavior

Successful transmission to vectors is required to conclude that an increased attractiveness of infected hosts is an adaptive strategy of the parasite. Three main steps lead to transmission and could be influenced by parasites: attraction of vectors, vectors' decision to bite, and vectors' ability to bite, determined mostly by hosts' defensive behavior. Experiments aiming at determining whether parasites make their host more attractive to vectors use diverse methods, which sometimes does not allow addressing, or differentiating between, each step of this process. **Supplementary Figure S1** summarizes study main results in function of experimental characteristics.

A major difference between studies is whether uninfected and infected hosts attractiveness is compared through dual-choice experiments or through comparisons of biting/attraction rates. In dual-choice experiments, vectors are offered equal numbers of infected and uninfected hosts (in general, one of each) simultaneously, either in a dual-choice olfactometer (e.g., Lalubin et al., 2012), where vectors are not allowed to bite, or in a cage (e.g., Cornet et al., 2013a,b) or arena (e.g., van Duijvendijk et al., 2016). Dual-choice olfactometers have the advantage of allowing a distinction between attraction and vectors' ability to bite and providing direct evidence that one category of hosts is more attractive than the other. They also allow using only host odor, carbon dioxide emission or individual volatile compounds and test the relative attractiveness of each molecule. Nevertheless, dual-choice olfactometer experiments should, when possible, be coupled with dual-choice experiments where vectors are able to bite. Indeed, a higher attraction does not necessarily translate into more blood meals. We can conclude that the apparent manipulation is adaptive only by showing that infected hosts get more bites and transmit their parasites.

Allowing animals to defend themselves against vectors during experiments admittedly provides a better representation of the process in the way it would happen in the wild. However, when infected hosts differ in their behavior due to sickness, they become in general less active and less defensive, which facilitates vector attacks (Day et al., 1983; Turell et al., 1984; Coleman

et al., 1988). Thus, in this setting, a higher biting rate of infected host cannot be conclusively assigned to either sickness behavior, which may be associated with a decrease in defensive behavior, or parasite manipulation of host attractiveness. For example, *Plasmodium yoelii*-infected mice and *P. yoelii* + *Leishmania mexicana* - infected mice were less active during the peak infection and this coincided with a peak in the number of mosquitoes able to take a blood-meal (Coleman et al., 1988). Day et al. (1983) found an association between gametocyte density, defensive behavior and mosquito biting success in *P. chabaudi*- and *P. berghei*-infected mice. This type of change in behavior of infected animals is sometimes regarded as a type of parasite manipulation (Lefèvre and Thomas, 2008). While it can be coincidentally advantageous for parasite transmission, sickness behavior may have evolved as an adaptive strategy in hosts, increasing the probability to eliminate or recover from the infection (Hart, 1988; Johnson, 2002), rather than a part of parasite extended phenotype. Indeed, sickness behavior is triggered by the immune response, in particular cytokines, and can be induced by the injection of lipopolysaccharide without the actual presence of parasites (Dantzer, 2001). Thus, this response is not specific to any parasite, which supports the idea that this consequence of infection has not evolved as a parasite adaptation but is under the genetic control of the host. Adamo (2014) has formulated the hypothesis that sexually transmitted pathogens suppress sickness behavior, which generally includes loss of sexual motivation, thus favoring their transmission. It would seem that inhibition of sickness behavior is more likely to result from parasite manipulation than the opposite.

When trying to determine whether a parasite adaptively manipulates the attractiveness of its host, experiments should as much as possible decompose each step of the process to properly identify whether infected hosts are really more attractive, whether they really get more bites and whether bites really result in transmission. One way to test whether infected hosts get more bites, while avoiding the confounding factor of defensive behavior, is to anesthetize the tested animals (da Rocha Silva et al., 2019) or to mechanically immobilize them (Cornet et al., 2013a,b).

Natural Versus Experimental Infections

The possibility of observing parasitic manipulation of host attractiveness may depend on the level of co-adaptation in the host-vector-parasite trio. If being infected bears a fitness cost for vectors, they might evolve parasite avoidance strategies. Evidence for impacts of parasites on their arthropod vector reproductive parameters exist, especially in mosquitoes, although they are sometimes contradictory. Using lab-bred *Culex pipiens* and *Plasmodium relictum*, infection was shown to decrease mosquito fecundity (Vézilier et al., 2012; Pigeault and Villa, 2018) and to increase their survival under *ad libitum* food conditions (Vézilier et al., 2012). On the opposite, using mosquitoes reared from egg rafts collected in the field, the same infection was shown to slightly increase fecundity (Delhaye et al., 2016) and to decrease survival under a food restriction regime (Lalubin et al., 2014). Independently of the systems used,

most of these studies did not find an effect of the infection on host longevity when food was given *ad libitum* (Lalubin et al., 2014; Delhayé et al., 2016; Pigeault and Villa, 2018). Moreover, *Plasmodium falciparum* increases fecundity and do not reduce survival in *Anopheles gambiae* (Alout et al., 2016). Evidence for cost of infection in other vector groups are less numerous; *Trypanosoma cruzii* infection decreases fecundity and survival of the triatomine bugs *Meccus pallidipennis* (Cordero-Montoya et al., 2019). Conflicting results regarding the manipulation of host choice by vector-borne parasites could result from differences in the associations of species tested (natural or not), as well as in the origin of the tested individuals, wild or laboratory-bred (Ferguson and Read, 2002; Tripet, 2009).

It may thus be possible that vectors and parasites face off in an evolutionary arms race between parasite avoidance and deceptive signaling. If this is the case, when we observe interactions between populations that are co-evolving, vectors' potential anti-infection mechanisms might counteract parasite manipulation, depending on what stage of this arms race they are experiencing. In addition, we need to consider the release from selective pressure allowed to lab strains as potentially enhancing or reducing the effect of parasite on attractiveness. Indeed, lab-bred mosquito populations that have not been under selective pressure for parasite resistance/avoidance for hundreds of generations – as they are usually fed on uninfected blood sources – might show exacerbated attraction to hosts whose attractiveness has been manipulated by parasites. Alternatively, they might have lost some host-seeking skills by being constantly offered effortless food. Similarly, parasite strains that have been passaged across several years without the contribution of vectors (e.g., by intraperitoneal injections of infected host blood into another host) might have lost their capacity to make their hosts attractive to vectors. This might explain the discordant results of Lalubin et al. (2012) and Cornet et al. (2013b), who found a lower attraction of *Culex pipiens* toward wild great tits (*Parus major*) naturally infected by *Plasmodium sp.* and a higher biting rate in canaries infected with a lab strain of *Plasmodium relictum* (SGS1), respectively. In addition to the infection origin and the variable measured, these experiments differ with regards to the mosquito origins, as Lalubin et al. (2012) used mosquitoes emerged from freshly collected egg rafts, present at one of the sites where the tested great tits were caught, while Cornet et al. (2013b) used a lab colony initiated 10 years before the experiment. The generally reduced phenotypic variation of lab strains and the release from co-evolutionary selection pressures (Tripet, 2009) can explain the diverging results of these two experiments.

The expectation that mosquitoes should experience selection for parasite avoidance needs to be mitigated by two considerations. First, if the cost of seeking a new – hopefully uninfected – host exceeds the cost of being infected, evolution for parasite avoidance is unlikely. This could depend, among other factors, on host density and availability, and on parasite prevalence. Secondly, if the only effects of infection perceivable by vectors are quantitative variations of existing cues always used when host seeking, for instance the increased production of some

VOCs (de Moraes et al., 2014; de Boer et al., 2017; Robinson et al., 2018), it might be more difficult for vectors to evolve parasite avoidance. They could rely on other cues, for instance the detection of a particular skin microbiota composition after landing on host, however, the mechanisms of this hypothetical detection is unknown to the best of our knowledge.

The Importance of Controlling for Co-infections

When comparing the attractiveness of uninfected and infected hosts, it is crucial to take into account the possibility of co-infection with other parasites. It is especially important when using naturally infected individuals, in particular if several parasites are locally transmitted by the same vector species. For example, none of the studies examining the attractiveness of wild *Plasmodium*-infected birds to *Culex pipiens* shown in **Table 1** tried to determine whether the birds were harboring West Nile Virus (WNV), which is also transmitted by *Culex pipiens*. This could be a concern especially if these parasites co-occur in a non-random way, as it was found to be the case in Chicago, where there was a negative association between *Plasmodium sp.* infections and WNV serostatus (Medeiros et al., 2014). By ignoring other potential infections, we might under- or overestimate the capacity of the focal species to increase its hosts' attractiveness.

On Using Anti-malarial Treatment to Have Uninfected Controls

Most studies comparing infected individuals and individuals after anti-parasite treatments found a preference for non-treated individuals (Lacroix et al., 2005; Batista et al., 2014; Busula et al., 2017a; Robinson et al., 2018; Yan et al., 2018; but see de Boer et al., 2017). Using treated individuals as uninfected controls is convenient for assessing the attractiveness of naturally infected hosts when uninfected hosts are difficult to find. It also allows avoiding a pre-existing bias, in the sense that naturally uninfected individuals might be so because they are, for other causes unrelated to the focal infection, less attractive to vectors (Mukabana et al., 2002). However, anti-parasitic drugs can have an effect on biting insects, independently of their infection status, either through a direct effect or through an alteration of blood characteristics. A preference for infected hosts in this type of experiments might actually indicate an avoidance of drug-treated hosts. In a recent study, de Boer et al. (2019) evaluated the effect of artemether-lumefantrine (AL) on mosquito host-seeking behavior and fitness. Using traps baited with socks worn by AL-treated men (before, during and after treatment) they found more *Anopheles coluzzi* attracted to the socks worn after treatment, but no difference between before and during treatments. In a semi-natural setting, *Anopheles gambiae* did not show a preference for either AL treatment time-points. However, a comparison of the attractiveness of socks worn the same day by AL-treated and untreated humans would have been useful to avoid an effect of “time since odor collection”. Membrane-feeding with human blood containing a high concentration of dissolved AL resulted in no difference

in survival, oviposition rate, timing before oviposition and number of eggs. This tends to suggest that it is appropriate to use AL-treated individuals as “uninfected” hosts in mosquito choice trials. Nevertheless, studies allowing mosquitoes to feed on infected+untreated, uninfected+untreated, infected+untreated and uninfected+untreated humans are necessary to conclude, because metabolization of AL might induce changes in blood characteristics that would not occur in membrane-feeders. Lacroix et al. (2005) found that former gametocyte carriers treated with sulfadoxine pyrimethamine (SP) seemed to repel mosquitoes, although it was not the case of treated individuals that were not gametocyte-carriers. As high concentrations of SP can strongly reduce *Anopheles stephensi* survival (Kone et al., 2010), mosquitoes might evolve the capacity to detect and avoid SP-treated humans.

Potential for Publication Bias

Parasitic manipulation of host attractiveness is a seducing hypothesis and publication bias is likely to occur, as was suggested by Poulin (2000). Among the studies presented here, those that found a preference for infected hosts were on average more cited than the studies finding a preference for the uninfected host, and both were more cited than studies finding no preference (Supplementary Figure S2). This might discourage researchers to submit (and publishers to publish) manuscripts reporting results that do not support the hypothesis of increased attractiveness of infected hosts.

PERSPECTIVES

Future work on this topic could use the selection of studies reviewed here to conduct a meta-regression aiming to quantify the magnitude of the effects. Indeed, while we discussed the potential influence of different experimental designs on effect directionality – i.e., the preference of vectors for infected versus uninfected hosts – a meta-regression would provide a formal testing of their impacts on the strength of the observed effect in a quantitative way. This would also allow a more accurate identification of possible publication bias. Finally, a meta-regression could be used to assess to what extent different transmission cycle characteristics or parasite life history strategies affect vector-borne parasite manipulation of host.

CONCLUSION

This review highlights that manipulation of host attractiveness is widespread among different groups of vector-borne parasites. However, contradictory results show that it cannot be considered as a rule. Manipulation of host attractiveness might be one side of an evolutionary arms race against parasite avoidance, and different pairs of vector and parasite populations could find themselves at one or the other stage of a co-evolutionary timeline. In addition, parasites other than *Plasmodium sp.* deserve that we put more effort into investigating their ability to trigger attractant molecules production in their hosts, especially vector-borne viruses and filarial worms. Experiments trying to assess

the generality of this phenomenon should ideally design their experiment in a way that (1) verifies the presence of transmissible stages in host blood, (2) separates attraction from capacity to bite, and (3) uses parasite and vector strains that have not been released from co-evolutionary selective pressures for many generations. Finally, we stress the importance to investigate the proximate mechanisms responsible for a higher attractiveness of infected hosts in order to determine which partner has the genetic control of the situation, as well as its impact on parasite fitness, before concluding on adaptive manipulation (Herbison et al., 2018).

AUTHOR CONTRIBUTIONS

C-SC, OG, PC, and RP contributed to the original idea and the final version of this manuscript. C-SC and RP collected the data and contributed to the first draft of this manuscript. C-SC conceived the figures and analyzed the data. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: <https://www.frontiersin.org/articles/10.3389/fevo.2020.568140/full#supplementary-material>

FIGURE S1 | Study main results in function of experimental characteristics. This figure summarizes the number of studies that found a greater attraction of infected vertebrate hosts according to different experimental characteristics (natural versus experimental infection, host defensive behavior possible or not). This figure does not account for effect sizes.

FIGURE S2 | Number of citations of the reviewed studies in function of the year of their publication. The regression lines were plotted using the “ggplot” package (Wickham, 2016), using values predicted by a negative binomial generalized linear model, using the number of citations as the response variable, and the year of publication and the main result as predictors (orange: at least one result of the study shows a higher attractiveness of infected hosts; blue: at least one result of the study shows a higher attractiveness of uninfected hosts; green: no difference found). We used the function *glm.nb* in the “MASS” package (Venables and Ripley, 2002) to fit the model. The likelihood ratio test was used to assess the significance of both predictors: “year of publication”: $\chi^2_1 = 3.73$, $p = 0.053$; “main result”: $\chi^2_2 = 6.69$, $p = 0.035$. We also fitted a model with an interaction between the year of publication and the main result, and the interaction was not significant ($\chi^2_2 = 2.15$, $p = 0.34$). Analyses were performed on R v.3.5.1 (R Core Team, 2018).

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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