Infection prevalence and vector-borne transmission: are vectors always to blame?

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The potential for vector-independent transmission of pathogens to occur in what is generally considered to be a vector-borne system is a subject that has received little direct attention. The circumstances under which such a process might take place could conceivably be described as ‘occasional’ under natural conditions and ‘accidental’ under unnatural conditions. A more immediate concern is the ability to detect the presence of vector-independent transmission in action and, where possible, to quantify its contribution to overall infection prevalence. As intrinsically difficult as this process might be, careful observation and the use of laboratory and field-scale experiments have indicated that alternative, vector-independent routes of transmission do exist and might contribute significantly to overall prevalence in some host–vector–pathogen systems.

Accidental and occasional transmission

Broadly speaking, transmission pathways are considered to be vector dependent or vector independent (including direct and indirect transmission) (see Glossary), but rarely both. As such, epidemiological models are developed accordingly and, thus, risk overestimating the transmission potential of arthropod vectors, or underestimating the possibility of alternative or ecologically based drivers in maintaining what is otherwise considered a vector-dependent infection. The difficulty lies in the fact that alternative routes of transmission might be 'accidental' and, therefore, unexpected and difficult to detect; they might result, for example, from faecal contamination or aggression during artificially high stocking densities within commercial populations. Other examples of alternative transmission, which might be equally difficult to detect, can be considered as 'occasional' occurrences that happen under more natural conditions. These occurrences could be linked ecologically to temporal changes in host behaviour (such as increased aggression during the breeding season), or climate and/or resource driven (such as prey switching or cannibalism) and, therefore, might act to drive infection prevalence above that possible by vector-dependent transmission alone. Furthermore, the distinction between accidental and occasional occurrences is often cryptic and difficult to determine, resulting in potential confusion. Hence, there is a need to clarify the issue where possible.

Recognizing alternative transmission in action

Often, a key component in establishing the presence or absence of alternative transmission is recognizing an anomaly that indicates its existence within a system. The discovery of West Nile virus (WNV) in a dead hawk in New York, USA, during the winter of 2000 raised concerns because it was immediately apparent that its presence could only be explained by

one of three scenarios [1]: (i) that WNV was transmitted by an infected arthropod vector during midwinter; (ii) that the hawk had acquired the virus from a vector earlier, and the virus had remained latent until it caused the death of the bird; or (iii) the hawk acquired the infection by killing and eating an infected reservoir host. Considering the acute pathology of WNV and the time of year when the hawk died, all indications were that option (iii) was the most likely and the hawk acquired WNV directly without the involvement of an intermediate vector (i.e. that this was an example of an 'occasional' transmission episode). Subsequent experimental investigations have shown that vector-independent transmission of WNV can occur among geese and that this was the most probable cause of loss in a commercial stock of geese over and above that explainable by mosquito-borne transmission alone [2]. The alternative route of transmission in this case was believed to be a result of feather picking and the cannibalism of a sick goose or geese, which in an unnaturally high-density environment would equate to 'accidental' transmission. Furthermore, in some host species, including geese, direct transmission can result in viraemic titres that are sufficiently high to reinfect feeding mosquitoes and, thus, further perpetuate the cycle [3]. A more comprehensive review that covers vector-independent transmission of a range of arboviruses is given by Kuno [4].

Vector-independent transmission of parasites

The degree to which vector-independent transmission contributes to the overall prevalence of a parasite in a susceptible population is difficult to determine. Vector-dependent transmission is generally determined by the rate of contact between infected hosts and susceptible vectors, and from infected vectors to susceptible hosts. This contact rate is assumed to increase in proportion to the density of hosts and vectors and, therefore, is considered to be 'density dependent' 5 and 6. Vector-independent transmission of otherwise vector-dependent parasites

also seems to act in a density-dependent manner but independently from the density of vectors. It is possible, therefore, that within some systems there is a host-density threshold above which changes in behaviour (for example, increased aggression) or the frequency of contact rates between individuals (for example, seasonal mating) result in additional opportunities for vector-independent transmission of a parasite to occur. Nonetheless, it is correct to assume that a vector-dependent parasite that undergoes a developmental stage within the vector will quickly die out in any transmission cycle that does not involve the vector; however, there are exceptions. The caecal worm *Heterakis gallinarum* (or another suitable paratenic host, such as an earthworm) might be necessary only for the initial introduction of the protozoan *Histomonas meleagridis*, the causative agent of blackhead disease in turkeys and other poultry, into a susceptible population because direct transmission might be sufficient to not only maintain but also spread infection throughout an entire flock [7]. For example, it has long been known that *H. meleagridis* was often prevalent in commercial pens, but early experiments to evaluate the oral transmission route were inconclusive, and it was assumed that alternative vectors must be involved [8]. It now seems that a single infected bird introduced into a flock can initiate an infection via what is known as cloacal drop 9 and 10. Although cloacal drop is a natural developmental behaviour in turkeys, this mode of vector-independent transmission of *H. meleagridis* can be considered an example of ‘accidental’ transmission because it arose primarily as a consequence of artificially high stocking densities within commercial pens that resulted in unusually high contact rates with infected faeces.

The parasite *Leishmania infantum*, the etiological agent of canine and human visceral leishmaniasis, is endemic within foxhound kennels in the USA. Transmission of *L. infantum*, like most *Leishmania* spp., has often been thought to be carried out exclusively by blood-

feeding phlebotomine sandflies [11]. However, *L. infantum* is found in kennels that are located in areas where suitable vectors are thought to be absent, or present in very low abundance. In addition, the observation that *L. infantum* was more prevalent within an index kennel among foxhounds that had travelled to the south-eastern USA indicated that an initial infection, most likely acquired via the bite of a sandfly, was being maintained and transmitted in the absence of vectors via an unidentified secondary route [12]. The potential secondary pathways include direct transmission between infected and uninfected individuals, in addition to congenital transmission. For example, Rosypal and Lindsay [13] reported that female BALB/c mice that were experimentally inoculated with *L. infantum* isolated from a naturally infected foxhound from Virginia (LIVT-1 strain) passed the infection on to four of 88 pups and, also, to one of the males used for breeding. Furthermore, it has also been shown that female beagles chronically infected with the same LIVT-1 strain can pass the parasite to their pups [14].

Therefore, experimentally, it seems to be possible for *L. infantum* to be transmitted via two alternative routes: (i) maternally from mother to offspring, and (ii) directly between male and female adults during mating. The implications of this are considerable with regards to animal welfare and human health, and highlight the potential for ‘occasional’ transmission of a parasite within a population that is otherwise considered safe from infection because of the absence of suitable vectors. A particularly relevant example of this is the locally acquired infection of cutaneous leishmaniasis that was reported in a red kangaroo (*Macropus rufus*) in Australia [15]. Before this discovery, endemic forms of leishmaniasis were considered to be absent from Australia, and the probability of establishment was considered to be small because of the presumed absence of competent sandfly vectors. Now, however, it seems that there is a possibly novel and persistent *Leishmania* spp. being transmitted either by an as-yet

unidentified vector or directly between hosts in a vector-independent cycle. There is also the potential that parasite evolution might result in an incidental host species (one that can be infected but cannot transmit a pathogen to a new host) becoming a reservoir host species and, therefore, capable of transmitting a pathogen, thus adding to the dynamic feedback of leishmaniasis in the region 16, 17 and 18. This also raises the possibility that if there is a vector involved in the transmission of this novel form of *Leishmania* to kangaroos, then presumably the same vector could transmit an introduced exotic pathogenic species.

Vector-independent transmission in wildlife populations

One approach to determining whether vector-independent transmission of a parasite occurs within a wildlife population is to conduct a controlled manipulative field-scale experiment. This approach is only feasible if the study system is suitable in terms of the distribution and abundance of the organisms under consideration, with small high-density hosts and abundant vectors and parasites being the optimum. Such a system was utilized by Smith *et al.* [19] in their longitudinal investigation into the role of direct transmission of the flea-transmitted protozoan *Trypanosoma microti* among natural populations of field voles (*Microtus agrestis*) in the UK.

T. microti is a host-specific blood parasite of field voles in which the developmental cycle is completed in the hind gut of a suitable flea vector, and infection occurs primarily via the contamination of the bite wound by infective-stage metacyclic trypomastigote forms shed in flea faeces 20 and 21. An observational study in which two populations of field voles were monitored over a two-year period showed that flea dynamics followed a seasonal pattern,

with peak infestation occurring during the summer (April–October) [19]. Trypanosome prevalence was also modelled and was shown to follow a similar seasonal pattern to flea vectors. The linear nature of the generalised linear mixed modelling (GLMM) technique meant that it was possible to remove the additive effect of fleas from the full explanatory model and deduce a hypothetical prevalence of trypanosomes in the absence of vectors. The results indicated that fleas were not the only source of infection and a significant degree of trypanosome infection would remain within the field vole populations in the absence of vectors.

To investigate further, Smith *et al.*[22] monitored two adjacent ‘experimental’ populations, within which each individual field vole was treated with a topical application of insecticide to reduce the prevalence and abundance of flea vectors. Their results show a clear and rapid reduction in the prevalence of fleas after the onset of treatment [22]. However, trypanosome infection was still present, at approximately one-third of the prevalence observed in control populations, as predicted by the statistical model. A further investigation indicated that the probability of trypanosome infection was highest for field voles that had recently entered the population, indicating that the remaining prevalence could be the result of a persistent infection that originated from contact with vectors outside of the treatment area. However, even when the analysis focused specifically on individuals that were known to be negative on first capture (and was, thus, reflective of the ‘resident’ or ‘treated’ population), trypanosomes were still present, which indicated that persistent infection played only a minor part in maintaining *T. microti.*

Therefore, it seems that direct transmission might be responsible for up to one-third of the observed prevalence of *T. microti* within field voles under natural conditions. This observation is striking because it indicates that not only does vector-independent transmission occur on more than just an 'occasional' basis but also it might do so to a biologically important degree. This assertion is supported by several factors that are related to the development cycle of the trypanosome parasite (Figure 1) and to field vole ecology; these factors include the observation that field voles can be experimentally infected with *T. microti* via contamination of the oral-mucal membranes with infective metacyclic trypomastigotes [23] and that the opportunity for direct transmission of infective stages exists as a result of aggressive interactions during the breeding season [24]. However, it is recognized that flea-mediated transmission is ultimately necessary for *T. microti* to persist, and in the complete absence of fleas over a wider area than that surveyed by Smith *et al.*[22], trypanosome prevalence would equilibrate at a much lower level or disappear altogether.

Does it happen, and does it matter?

Although it is perhaps intrinsically difficult to detect and quantify, evidence indicates that in some systems vector-independent transmission of vector-dependent parasites or viruses does occur and seems to do so to a considerable level. Tell-tale indications might indicate the potential for direct transmission to be a factor in other host–parasite systems. For example, the observations that infective-stage trypomastigotes of *T. cruzi* were present in the anal glands and excreta of opossums [25], and opossums can become infected with *T. cruzi* via the oral route [26] indicate the potential for a vector-independent cycle that maintains *T. cruzi* by contamination in areas where vectors are absent or present in low numbers [27].

The importance of vector-independent transmission remains to be determined, and untangling its effects from those of other epidemiologically confounding factors, such as climate 28, 29 and 30 and the ecological and immunological effects on disease transmission, is essential (see, for example, Ref. [31]). Understanding the effects of environmental degradation on disease transmission is equally important. For example, habitat fragmentation and the loss of biodiversity within forested regions of the eastern USA have resulted in an increase in the abundance of small rodents, which are highly competent reservoir hosts for both the spirochete bacterium that causes Lyme disease and the larval ixodid ticks that transmit it. Subsequently, there has been an increase in the abundance of ticks and the prevalence of infected ticks within the tick population, both of which lead to an increased risk of Lyme disease in humans 32, 33 and 34. The same seems to be true for American cutaneous leishmaniasis in low-diversity agricultural areas on the fringes of fragmented forests in Costa Rica, perhaps indicating a more general trend in host–vector–parasite ecology 35 and 36.

The experimental perturbation of a system away from equilibrium, either via a reduction in vector abundance or by providing hosts with a degree of protection from vectors, thus reducing host–vector-contact rates, is a robust method for determining the existence of vector-independent transmission within vector-dependent systems. Appropriate mathematical modelling can be used to identify systems within which vector-independent processes might be acting [37] and can provide the additional benefit of theoretically investigating the effects of varying host population densities, which might be particularly beneficial in commercial environments 38 and 39. However, the importance of vector-independent transmission remains to be determined and can only be fully appreciated once its existence has been established.

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Figure 1.

Vector-dependent and vector-independent transmission of a *Trypanosoma* sp. parasite. **(a)** During vector-dependent transmission, a vector becomes infected after the uptake of infective-stage trypomastigote forms in a bloodmeal obtained from a previously infected host. Within the vector, trypomastigotes develop further into epimastigotes before releasing infective trypomastigotes in faeces during feeding. An uninfected host becomes infected via contamination of the bite wound or ingestion of infective stages. **(b)** A vector-independent cycle is possible when trypomastigotes are passed directly from an infected host to an uninfected host during, for example, the aggressive interactions over mates or territory that can occur during the breeding season.