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The Epidemiology and Evolution of Symbionts with Mixed-Mode Transmission

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Abstract

Vertical and horizontal transmission are terms that describe the transfer of symbionts from parents to offspring and among unrelated hosts, respectively. Many symbionts, including parasites, pathogens, mutualists, and microbiota, use a combination of both strategies, known as mixed-mode transmission (MMT). Here I review what is known about the evolution, ecology, and epidemiology of symbionts with MMT and compare MMT with our expectations for single-mode strategies. Symbionts with MMT are common and, in comparison with single-mode symbionts, show many surprising features. MMT combines the best of two worlds with regard to the ecological conditions required for persistence and plays a role in the evolution of virulence and genome architecture. Even rare transmission by the minority type of these two transmission modes can make a big difference for the system. This review explores the conceptual issues surrounding the dynamics of mixed-mode symbionts by reviewing literature from the entire range of host and symbiont taxa.

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1. INTRODUCTION

Symbionts, here defined to include mutualists, commensals, parasites, and pathogens, live on a resource with finite life span, the host. Therefore, to persist in the long term, symbionts must be transmitted from host to host. Transmission is usually categorized as either horizontal or vertical. Vertical transmission (VT) is the passage of the symbiont from the host mother (sometimes the father) to its offspring, whereas horizontal transmission (HT) is the passage among hosts not related in a vertical line (Fine 1975) and may include sexual or environmental transmission. The mode of transmission influences such factors as the persistence and spread of the symbiont over time and space, the evolution of virulence, host-symbiont coevolution, the evolution of genomic architecture, and the cospeciation of hosts and symbionts. In many cases, however, VT and HT are not mutually exclusive, as many symbionts are able to do both; this is known as mixed-mode transmission (MMT). MMT is common in nature and in human symbionts and plays a profound role in the ecology and evolution of hosts and symbionts. This role and the evolution of the modes of transmission are the focus of this review.

Evolutionary and epidemiological concepts have been developed primarily for symbionts with exclusive VT or HT. How these concepts apply to systems with MMT is less studied. Does a symbiont that combines two modes of transmission have the best of two worlds? Are the evolution and ecology of MMT symbionts qualitatively different from single-mode symbionts? Is there a continuum between the extremes of pure VT and HT? Which conditions favor the evolution of one mode over the other, and when do their relative rates change?

To answer these questions, the epidemiological and evolutionary concepts associated with each mode of transmission must be explored. Most important is the relationship of VT and HT with host density. HT typically increases with host density, whereas VT is most efficient when host fecundity is high, which occurs typically under low-density conditions. Thus, symbionts with HT and VT persist under a wider range of ecological conditions than those with single-mode transmission (Lipsitch et al. 1995b). Likewise, parasites transmitted vertically to diapausing stages, such as eggs, larvae, or seeds, may survive periods of no HT and persist in such populations. Another evolutionary aspect associated with transmission mode is the frequency of hosts infected with multiple symbiont genotypes (Frank 1996b). Under exclusive VT, the likelihood of multiple infections is strongly reduced. When HT is possible, multiple infections become more frequent and play a decisive role in symbiont genome evolution and the evolution of virulence.

Modes of transmission are also subject to evolutionary change. Experimental evolution and comparative studies document the high evolutionary potential of transmission modes and challenge us to predict the optimal mode of transmission for different conditions. Host demographic and epidemiological conditions influence the opportunities for transmission by one mode or the other, giving differential evolutionary weight to different transmission strategies. Here I review what is known about the evolution, ecology, and epidemiology of symbionts with MMT and compare MMT with our well-known expectations for single-mode strategies.

2. TRANSMISSION

2.1. Defining Vertical and Horizontal Transmission

The terms VT and HT were introduced to distinguish between parental and nonparental transmission, independent of the physical route of transmission (Fine 1975). More broadly, VT includes any form of maternal or paternal transmission, although it is mostly used to describe

uniparental transmission, which is predominantly maternal. VT is also used for certain physical routes of transmission between mothers and offspring, such as transmammary, transovum, transovarial, transplacental, and intrauterine transmission. In contrast, other physical routes, such as sexual, vector-borne, and attendant-borne transmissions are classified as HT. However, although a symbiont's physical route of transmission often defines its mode of transmission, some physical routes—for example, transmission in a social context (e.g., during parental care, social interactions, and spatial structure)—can be both vertical and horizontal. VT by routes more typically associated with HT has been variously called social transmission, pseudo-VT, external maternal transmission, postnatal VT, and postzygotic VT (Mims 1981, Wilkinson 1997, Moran et al. 2008). Furthermore, symbionts with VT have been described from diverse taxa, not only from those with intracellular lifestyles (e.g., viruses, microsporidia, and many bacteria), which are thought to predispose symbionts to VT. Thus, judging the mode of transmission by the observed physical route of transmission or by the lifestyle of the symbiont can be misleading. Here I call any form of parent-offspring transmission, regardless of the physical route or the symbiont's lifestyle, VT.

Taking this definition to the population level reveals an important relationship between VT and both the family structure of a population and the population size. Family structure produces more possibilities for parent-offspring contact within a host population and thus more VT than would be expected by random transmission. But even without any family structure, some mothers will transmit a symbiont to their offspring, and the smaller the population size, the more likely this is to occur. In this review I consider VT only for cases in which its occurrence is more frequent than would be expected from random transmission among hosts with the same total population size.

2.2. Using Population Genetics Tools to Detect Transmission

Enabling researchers to identify VT, population genetic tools were used to find the cotransmission of host and symbiont genes, which makes the study of symbionts entirely independent from the knowledge of the physical routes of transmission. Population genetics tools have also allowed researchers to detect HT and VT events so rare that conventional methods would not detect them. During VT, symbiont alleles become associated with host alleles (Wade 2007). These associations can be detected as interspecies linkage disequilibrium, i.e., certain combinations of host and symbiont alleles are found together more often than chance would predict (Sanchez et al. 2000). VT results in congruence between host and symbiont pedigrees and, in the most extreme form, in congruent host and symbiont phylogenies. HT breaks associations between host and symbiont alleles, whereas VT preserves them. However, the absence of interspecies linkage disequilibrium does not necessarily demonstrate that VT is absent, as relatively small amounts of HT can degrade the linkage signal (Brandvain et al. 2011). Interspecies linkage disequilibrium is also produced by other mechanisms; for example, selection may influence the frequency of certain allele combinations. Furthermore, the spatial structures of both partners, host-symbiont codispersal, genotype-specific habitat choice, assortative mating, host-genotype by symbiont-genotype interactions, and inbreeding can all influence interspecies linkage disequilibrium as well (Wade & Goodnight 2006, Wade 2007). When the genetic formulation of gene cotransmission is made explicit, one can examine these issues in great detail and draw conclusions about the ecology and evolution of the system (Wade 2007). The population genetics perspective also allows us to widen the concept of VT, disconnecting the physical process of transmission from its consequences for population genetics and evolution. Examples for this include transmission among relatives, e.g., social insects (Schmid-Hempel 1998), and transmission of selfish genetic elements (Smith 2007).

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2.3. Mixed-Mode Transmission

VT and HT can describe either individual transmission events or the sum of all a symbiont's transmission events within a host population, so that the mode of transmission is a statistical property. A symbiont can be called an MMT symbiont when infections produce secondary infections by both modes, even if the two forms of transmission do not occur from the same host individual at the same time or at equal frequency. Combining this with the definition for VT stated above, MMT occurs if the chances for HT are larger than zero and the chances for VT are larger than would be expected from random transmission among hosts.

Taking this definition of MMT into account will be important for the next generation of epidemiological and evolutionary models. However, in the context of this paper, I apply MMT according to traditional usage, i.e., cases with evidence from observational, experimental, or population genetics studies of VT and HT. This is because scaling rates of VT to the expectations from random transmission in a population of a given size is often impractical and not available for any system. This restricted usage of MMT does not affect the content of this review.

MMT is observed primarily in two forms. First, symbionts may be transmitted by more than one physical route. For example, the microsporidium *Hamiltosporidium tvaerminnensis* is transmitted transovarially to host offspring but simultaneously produces transmission stages that become waterborne and spread to unrelated hosts after the host's death (Haag et al. 2011). *Toxoplasma gondii*, which infects many warm-blooded animals, including humans, has three physical routes of transmission: oral uptake of oocysts shed by the definitive host (cat), trophic transmission (via carnivory), and mother-child transmission (Hide et al. 2009). Some vector-transmitted protozoan parasites such as the malaria agent *Plasmodium falciparum* and different *Trypanosoma* species also show maternal transmission in their human host (**Table 1**). Many vector-transmitted viruses, bacteria, and protozoa are vertically transmitted in their vector (**Supplemental Table 1**, for all **Supplemental Material**, follow the link from the Annual Reviews home page at **http://www.annualreviews.org**). In some cases, different physical routes of transmission may be used side by side from the same host individual; in other cases, different routes exclude each other, such as in lytic/lysogenic bacteriophages where VT relies on cell division but HT kills the host.

Second, and possibly more importantly for MMT, the symbiont uses the same physical route for both VT and HT. For example, the scabies disease agent, the mite *Sarcoptes scabiei*, uses person-to-person contact as a physical transmission route, which results in both parent-offspring VT (maternal and paternal) as well as HT, including sexual transmission. Further examples include mycorrhizae and fungal pathogens in plants, ectoparasites (e.g., skin mites, fleas, lice), and human pathogens (e.g., *Helicobacter pylori*, *Giardia lamblia*, hepatitis B) (**Table 1**). Here we also need to include the vast number of species belonging to the skin and gut microbiota of plants and animals (see sidebar, Microbiota Are Mixed-Mode Transmitted). Furthermore, many human diseases that spread within households, such as influenza, pinworms, scabies, head lice, and varicella, may also be included in this list. In these cases VT often occurs simply as a consequence of offspring being at some stage close to their mother and/or father.

Only transmission modes that contribute to the long-term gene pool of the symbiont population are of interest for their evolution, excluding infections that are not passed on to other hosts. For example, HIV is mainly transmitted sexually but is frequently passed to babies of infected mothers (Arnaiz-Villena et al. 2009). These infants, if untreated, die before the virus has the opportunity to transmit further. Thus, from an evolutionary perspective, VT of HIV is a dead-end road for the virus, although it is a matter of grave concern from a medical and public health perspective. The same arguments apply to the rubella virus and *Toxoplasma gondii*.

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Supplemental Material

Table 1 Examples of symbionts with mixed-mode transmission

Symbiont	Host	Physical route of VT/note on ST or PT[a]	Reference(s)
Viruses			
Lambdoid phages	*Escherichia coli*	Phage inserts in host genome	Refardt & Rainey 2010
Lettuce mosaic virus	Cultivated lettuce	Seedborne	Grogan et al. 1952
Sugarcane mosaic virus	Sugarcane	(?)/PT	Li et al. 2007
Granulovirus	Indian meal moth, *Plodia interpunctella*	(?)/PT	Burden et al. 2002
Nucleopolyhedrovirus	African armyworm, *Spodoptera exempta*	Transovum/PT	Vilaplana et al. 2008
Bovine immunodeficiency virus	Cow	Transplacental	Scholl et al. 2000
Human immunodeficiency virus, HIV (AIDS)	Human	During birth/PT, ST	Arnaiz-Villena et al. 2009
Hepatitis B virus	Human	During birth/PT, ST	Stevens et al. 1975, Hann et al. 2007
Human T cell leukemia virus	Human	Via breast-feeding/ST	Nicot 2005
Herpes simplex virus-1	Human	Skin contact/ST	Mark et al. 2006
Bacteria			
Holospora undulata (Bacteria)	Protozoan, *Paramecium caudatum*	Intracellular	Kaltz & Koella 2003
Hamiltonella defensa, *Regiella insecticola* (*Enterobacteriaceae*)	Aphid, *Acyrthosiphon pisum*	Transovarial/ST	Moran & Dunbar 2006
Paenibacillus larvae (bacteria, American foulbrood)	Honeybee, *Apis mellifera*	Social transmission	Fries et al. 2006
Wolbachia sp. (Bacteria)	Parasitic wasp, *Leptopilina clavipes*	?	Kraaijeveld et al. 2011
Asaia sp. (Bacteria)	Mosquito, *Anopheles stephensi*	?/ST	Damiani et al. 2008
Several species of *Rickettsia* (Bacteria)	Diverse arthropods	Mostly transovum	Weinert et al. 2009
Borrelia duttoni (Bacteria)	Tick, *Ornithodorus moubata*	?/PT	Wagner-Jevsseenko 1958
Bacterial symbionts	Vesicomyid clams	?	Stewart et al. 2008
Bacterial symbionts	Gutless marine oligochaetes	?	Giere & Langheld 1987
Bordetella pertussis (Bacteria, whooping cough)	Human	Coughing, sneezing	Bisgard et al. 2004
Helicobacter pylori (Bacteria)	Human	Social transmission/PT	Weyermann et al. 2009
Microsporidia			
Nosema (Perezia) fumiferanae (Microsporidia)	Spruce budworm, *Choristoneura fumiferanae*	Transovarial (?)/PT	Thomson 1958
Amblyospora connecticus (Microsporidia)	Mosquito (*Aedes cantator*) and copepod (*Acanthocyclops vernalis*)	Transovarial (?)	Dunn et al. 2000

(*Continued*)

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Table 1 (*Continued*)

Symbiont	Host	Physical route of VT/note on ST or PT[a]	Reference(s)
Nosema ceranae, *Nosema apis* (Microsporidia)	Honeybee, *Apis mellifera*	Social transmission	Schmid-Hempel 1998
Tubulinosema kingi (Microsporidia)	Fruit flies, *Drosophila melanogaster*, *Drosophila subobscura*	Transovum (?)	Futerman et al. 2006
Edhazardia aedis (Microsporidia)	Mosquito, *Aedes aegypti*	Transovarial	Agnew & Koella 1997
Hamiltosporidium tvaerminnensis (Microsporidia)	Waterflea, *Daphnia magna* (Crustacea)	Transovum	Haag et al. 2011
Fungi			
Neotyphodium endophyte	*Lolium multiflorum*	Seed transmission	Gundel et al. 2011
Protozoa			
Ophryocystis elektroscirrha (Protozoa)	Monarch butterfly (*Danaus plexippus*)	Spores deposited on eggs/PT	de Roode et al. 2009
Gut flagellates	Termites	Proctodeal trophallaxis	Desai et al. 2010
Toxoplasma gondii (protozoa)	Cat, diverse mammals	Transplacental (?)	Dunn et al. 1999, Hide et al. 2009
Giardia lamblia (protozoa, giardiasis)	Human	Social transmission	Wolfe 1992
Plasmodium falciparum (protozoa, malaria)	Human	Transplacental	Redd et al. 1996
Trypanosoma brucei (protozoa, African trypanosomiasis)	Human	Transplacental (?)	Lindner & Priotto 2010
Trypanosoma cruzi (protozoa, Chagas disease)	Human	Transplacental (?)	Scapellato et al. 2009
Nematoda			
Toxocara canis (nematode)	Dog, fox	Transplacental and breast feeding	Markell & Voge 2006
Arthropoda			
Dermanyssus gallinae (Acari, ectoparasitic)	Poultry and other birds	Social transmission	Clayton & Tompkins 1994
Sarcoptes scabiei (Acari; scabies, a skin disease)	Human	Social transmission/PT, ST	Wendelboe et al. 2007
Ceratophyllus gallinae, hen flea (Insecta, ectoparasitic)	Great tit, *Parus major*	Social transmission	Richner & Tripet 1999
Hirundoecus malleus (Insecta, chewing louse)	Barn swallow, *Hirundo rustica*	Social transmission	Moller et al. 2004

[a]Sexual transmission (ST) (a form of horizontal transmission) and paternal transmission (PT) in addition to maternal transmission are highlighted.
VT, vertical transmission.

2.4. Paternal Transmission

Transmission from fathers to their offspring is also a form of VT. Although understudied, paternal transmission (PT) is much less common than maternal transmission (Longdon & Jiggins 2010). Typically, symbionts with PT also have maternal transmission and in most cases also HT; hence, with few exceptions, they can also be classified as mixed-mode symbionts. Examples include diverse viruses (e.g., sigma viruses of several *Drosophila* species), some protozoa, microsporidia,

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MICROBIOTA ARE MIXED-MODE TRANSMITTED

Most organisms harbor microbial communities (i.e., microbiota) that occupy the body surfaces, digestive tracts, and other tissues of diverse hosts. For example, human microbiota are estimated to include a few-thousand microbe species (Ley et al. 2006) and play an important role in health (e.g., protection, nutrition, development) and disease (e.g., cystic fibrosis, obesity, autoimmunity). More generally, microbiota are important for the overall well-being of multicellular organisms (Dethlefsen et al. 2006, Ley et al. 2006, Zilber-Rosenberg & Rosenberg 2008).

Evidence is increasingly pointing toward mixed-mode transmission (MMT) as a dominant mode of microbiota transmission (**Supplemental Table 2**). Apart from a few transgamete-transmitted microbes in some host taxa, most organisms start their life without microbiota. During development, they acquire symbionts from their mother (or, more rarely, their father), other hosts, or the environment. It is now clear that many microbes are transmitted from mothers to their offspring. Maternal transmission of mouse microbiota is so stable over generations that kinship relationships are reflected in microbial community composition (Ley et al. 2006). However, microbiota of mothers and offspring are not completely identical, supporting the notion that they are mixed-mode transmitted.

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and bacteria (**Table 1**). PT of symbionts may occur during paternal care (e.g., microbiota, ectoparasite transmission) or may take an indirect route of sexual transmission from males to females (with sperm or pollen) and, subsequently, to their offspring (Mink 1993, Moran & Dunbar 2006, Damiani et al. 2008, Longdon & Jiggins 2012). Exclusive PT seems rare: A notable exception is the transfer of symbiotic fungi by a species of termite (Korb & Aanen 2003). If VT is uniparental, the same epidemiological and evolutionary models apply whether transmission is paternal or maternal. In most cases, PT rates are lower than maternal transmission rates (Altizer et al. 2004, Moran & Dunbar 2006, Damiani et al. 2008, Longdon & Jiggins 2010). As I discuss below, biparental transmission is distinct from uniparental transmission and profoundly changes the epidemiology of the system.

2.5. How Common Are Vertical and Mixed-Mode Transmission?

Exclusively VT symbionts are rare, possibly limited to obligate mutualistic bacteria of some invertebrate taxa (Moran et al. 2008, Bright & Bulgheresi 2010). The majority of symbionts often labeled VT (such as the reproductive parasites *Wolbachia* and many microsporidia) should, in fact, be considered MMT symbionts as they also have very low rates of HT (Dunn & Smith 2001, Moran et al. 2008, Werren et al. 2008, Brandvain et al. 2011). As I show below, a little bit of HT makes a big difference in symbiont evolution.

Compared to exclusively HT symbionts, how common are symbionts with MMT? Symbionts of humans allow us a rough estimate. The number of human nonzoonotic infectious diseases (approximately 550) (Taylor et al. 2001) combined with the species that make up the human microbiota (approximately 2,000) (Dethlefsen et al. 2006, Ley et al. 2006) yield a total count of approximately 2,500 symbionts. Microbiota are generally believed to be MMT (see sidebar, Microbiota Are Mixed-Mode Transmitted; **Supplemental Table 2**), suggesting that the overall proportion of MMT among human symbionts is high. Although we do not know the number of human nonzoonotic infections that have MMT, a count for viruses revealed that 50 of 228 (22%) human viral infections typically associated with HT also have some degree of maternal transmission (Taylor et al. 2001; K. Adair & M.E.J. Woolhouse, personal communication). This is an underestimate, as in most cases it does not include social transmissions between mother and

Supplemental Material

child. The proportion of MMT symbionts is likely to decrease if we include the 870 species of human zoonotic diseases (Taylor et al. 2001). Still, given the large number of microbiota, MMT symbionts may well represent the majority of all human symbionts, and the same may be true for other host taxa.

3. PERSISTENCE AND SPREAD

Symbionts with perfect uniparental VT must be beneficial to their hosts; otherwise their host line, on which they totally depend, would be outcompeted by uninfected hosts (Fine 1975). Alternatively, some predominantly VT symbionts persist by influencing host reproduction so that their representation in the next generation is higher than expected from a neutral nuclear allele in a sexually reproducing uninfected host. Examples for this are reproductive manipulators, which use sperm-egg incompatibility and induction of female-biased offspring sex ratios to persist (Dunn & Smith 2001, Werren et al. 2008).

Combining VT with HT enlarges tremendously the range of ecological conditions in which a symbiont can persist. Particularly key is that VT and HT relate differently to host density (Ebert & Herre 1996). HT increases with host density. By contrast, VT depends only indirectly on density: VT is highest when host reproductive success is highest (Lipsitch et al. 1996). Thus, symbionts gain the best of both worlds by combining two modes of transmission: They require lower minimal host densities to invade and persist in a host population, and they can reach much higher equilibrium prevalences. Indeed, MMT may explain how human parasites persisted in prehistoric hunter-gatherer societies in which densities and between-population contact rates were very low (Dobson & Carper 1996). Many agents of ancient human diseases, e.g., *Helicobacter pylori*, pinworms, lice, ticks, and several viruses such as hepatitis B, herpes, Epstein-Barr, and cytomegalovirus, have been reported to have MMT or are likely to have it through social transmission (**Table 1**). In host species with diapause or discrete generations, VT may allow the symbiont to endure during phases when HT is not possible. An extreme case is the Lettuce mosaic virus, which is transmitted to only a few percent of lettuce seeds (**Table 1**). Without this low amount of VT, the virus would go extinct during the winter, showing that even rare VT can be important for parasite persistence (Mink 1993). This knowledge is used in pest control, where surface sterilization of seeds (preventing VT) is an efficient way to reduce the likelihood of epidemics.

Ultimately, the MMT dual strategy greatly enlarges the range of conditions in which symbionts can persist and thus explains symbiont persistence where HT alone cannot. Other dual-transmission strategies similarly expand the parameters for persistence, e.g., the combination of sexual and nonsexual HT and the combination of direct host-to-host transmission with transmission from symbiont resting stages in the environment (Roche et al. 2011). Likewise, Fine (1975) pointed out that the combination of PT and maternal transmission allows persistence in a much wider parameter space. This explains why the biparentally transmitted sigma virus of *Drosophila* is able to persist and spread despite its virulence (Longdon & Jiggins 2012). More generally the benefits of added PT can be so significant that the symbionts would go extinct without it (Altizer & Augustine 1997, Altizer et al. 2004).

4. TRADE-OFFS BETWEEN VERTICAL AND HORIZONTAL TRANSMISSION

An increase in one mode of transmission may be associated with a decrease in another mode. Such trade-offs limit adaptation because evolution can reach only a balance between the two forms of transmission, but cannot maximize both. The shape and direction of correlations among

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transmission modes strongly influence symbiont dynamics, making transmission trade-offs very important in epidemiology (Lipsitch et al. 1995b, van Baalen 2000). A prerequisite for understanding transmission trade-offs is the quantification of VT and HT (**Supplemental Table 3**).

Supplemental Material

Two biological scenarios for trade-offs between VT and HT have been put forth. In some parasites, the release of HT stages is obligately associated with the death of the host and, thus, terminates VT (**Table 1**). Certain bacteriophages, for example, are capable of a lytic (HT) and a lysogenic (VT) life cycle, each of which excludes the other. Which form prevails depends on environmental conditions, with deteriorating conditions favoring phages with HT (Stewart & Levin 1984, Refardt & Rainey 2010). Other systems in which host death terminates VT and facilitates HT have been reported in the microsporidia of arthropod hosts and bacteria in a ciliate (**Table 1**). In some of these cases, the symbiont has to produce different types of transmission stages for the two modes of transmission, making trade-offs likely as the two forms of transmission exclude each other. A second scenario that can lead to trade-offs between VT and HT is based on the two modes' differing dependence on virulence. HT usually profits from increased production of transmission stages (Ebert 1998), but this high production of transmission stages may reduce the lifetime reproductive success of the host and, thus, VT (Bull 1994, Ewald 1994). Experimental evolution with viruses has pinpointed such trade-offs in hosts as different as bacteria and plants (Turner et al. 1998, Stewart et al. 2005), where selection for virus fitness under one mode of transmission led to a decline in the other mode.

However, trade-offs between transmission modes are not universal. In many systems, the rate of VT is directly linked to the production of transmission stages. For example, in the protozoan parasite *Ophryocystis elektroscirrha* of the monarch butterfly *Danaus plexippus*, higher replication rates increase the likelihood that the host's own eggs are exposed to the parasite (de Roode et al. 2009) at the same time that it also increases transmission to other hosts. This results in positive correlations between transmission-stage production, virulence, VT, and HT. Positive correlations between VT and parasite replication or parasitemia are also reported for HIV, human papillomavirus, *Trypanosoma cruzi*, and microsporidia (Kaye et al. 1994, McCarthy 1999, Hermann et al. 2004, van Frankenhuyzen et al. 2007). The same may be true for MMT members of the microbiota. Furthermore, positive correlations between VT and virulence have been observed in some systems (Kover & Clay 1998, van Frankenhuyzen et al. 2007), hinting at a positive correlation between VT and HT. More generally, positive correlations between VT and HT are expected whenever both modes of transmission rely on the same pool of transmission stages (e.g., parasite titer in host blood), which often results in the same physical route of transmission. In these cases, VT and HT are not two different traits, despite their different evolutionary and ecological implications.

A fundamentally different way to produce a trade-off between VT and HT is observed in systems with strong spatial structures, for example, in fig wasps laying eggs into fig fruits (Herre 1995), fruit flies laying eggs into mushrooms (Jaenike 2000), and entomopathogenic nematodes carrying symbiotic bacteria when infecting insect larvae (Sicard et al. 2004). In these systems, transmission within the structure (the fig fruits, mushroom, insect larvae) is considered to be random, as opportunities for transmission are limited by the local availability of hosts. If only one female reproduces in a patch, all transmission will be to her offspring (VT); however, as more females reproduce in this patch, the likelihood of more transmission to other hosts increases. HT and VT occur via the same physical route. In such spatially structured host populations, a negative correlation between VT and HT is found (Ebert & Herre 1996). When the relationship between the rates of VT and HT is determined by the host's population structure, selection acting on relative rates of transmission is constrained. Only changes in the host population structure can alter the relative proportion of VT and HT. In summary, correlations between VT and HT can have any sign and are determined by the physical route(s) of transmission and the population

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structure of the host. Trade-offs are more likely in cases in which different physical routes of transmission or strong spatial host-population structures occur.

5. HOST FIDELITY, BOTTLENECKS, AND CONGRUENT PHYLOGENIES

Some vertically transmitted symbionts have cospeciated with their hosts for many millions of years, so that their phylogenetic trees are highly congruent, i.e., the phylogeny of the symbiont mirrors that of its host. These patterns of strict congruent phylogeny have been seen in a number of bacteria and their invertebrate hosts (reviewed in Moran et al. 2008), with the oldest associations estimated to be more than 500 million years old (Gruber-Vodicka et al. 2011). These associations have evolved independently several times in diverse clades, but they seem to be restricted to obligate mutualistic interactions (Moran et al. 2008). Interestingly, strict congruent evolution is not always bound to transovarial transmission. Stinkbugs (*Plataspidae*) deposit the mutualistic gut bacteria on their eggs in the external environment. Transmission occurs when the newly hatched progeny ingest the bacteria (Hosokawa et al. 2006). The congruence of their phylogenetic trees suggests the absence of any HT for millions of years. Although this conclusion is supported on the between-host species level, it does not rule out HT among members of the same host species. However, congruent evolution has also been observed on the within-species level (Funk et al. 2000), suggesting that HT is absent. Such obligate mutualistic associations appear to be exclusively uniparental VT over long evolutionary time periods and may be the only systems for which this is the case (Moran et al. 2008).

Interestingly, obligate mutualists with strict uniparental VT show a range of genomic features that distinguish them from symbionts with even the slightest amount of HT, as judged from a lack of phylogenetic congruence of host and symbiont trees (Page 2003, Werren et al. 2008). These features include the smallest known sizes of bacterial genomes, very AT-rich genomes, lack of phages, lack of mobile elements, lack of genome rearrangements, and lack of gene uptake from the host (Moran et al. 2008). By contrast, facultative bacterial symbionts in insects either do not show these genomic features or show them in much less pronounced ways. These symbionts are not essential for their host, may be either mutualists (e.g., *Hamiltonella* in sap-feeding insects) or parasites (e.g., reproductive manipulators such as *Wolbachia*), and demonstrate more conventional genome features. Their phylogeny shows little or no congruence with the host phylogeny, testifying to at least some level of HT between hosts. HT may be so rare, however, that it is hardly detectable with direct methods to quantify transmission.

Two aspects of obligate, VT mutualists are believed to drive the evolution of the symbionts' specific genomic features: the apparent total absence of recent HT and the recurrent symbiont population bottlenecks during VT (Mira & Moran 2002). Together, these two elements reduce genetic variation among symbionts within a host. Genetic variance among symbionts within hosts creates a disadvantage for hosts (Frank 1996b), as within-host competition has been associated with higher virulence. By limiting the number of symbiont individuals that are vertically transmitted, the host is less likely to face within-host evolution of higher virulence (Frank 1996a). Such genetic bottlenecking is further enhanced by uniparental (as opposed to biparental) VT, which prevents mixing of lines of different descent (Hurst 1990), and by germ-line soma splits (Frank 1996a), in which a portion of the symbiont population is bottlenecked into the germ-line lineage where the host controls symbiont reproduction and thus keeps its genetic diversity low. The metabolically active soma lineage is not transmitted to the next generation. Obligate, but not facultative, bacterial symbionts of insects are often housed in a special organ in the host called the bacteriome, from which symbiont cells pass on to the host's offspring (Buchner 1965,

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Moran et al. 2008). The unusual genome features of obligate mutualists are believed to be a consequence of continuous bottlenecking of the symbiont population during VT, which increases genetic drift and the chances that deleterious mutations will go to fixation. This also reduces both the efficacy of purifying selection and lowers the probability that beneficial mutations will become fixed (O'Fallon 2007, Moran et al. 2008). Furthermore, reduced within-host evolution favors selection at the level of the host, giving a competitive advantage to hosts with symbionts with stronger beneficial effects. Increasing the transmission population size or adding rare HT would change both these effects drastically (O'Fallon 2007, Pettersson & Berg 2007, Dirks et al. 2012).

High interdependency between host and mutualistic symbionts has also evolved in many cases where HT is the predominant, or even the only, mode of transmission, such as in lichens, corals, sepiolid squid, and fish with bacterial bioluminescence, all of which disperse or are born symbiont free (Douglas 1994, Sapp 1994, Nishiguchi et al. 1998, Paracer & Ahmadjian 2000). These hosts are fully dependent on their symbionts, even though phylogenetic trees show little or no congruence. Thus, strict VT is not necessary for the evolution of obligate mutualism, but strict uniparental VT is found together only with obligate mutualism.

At one point, congruent phylogenetic trees between hosts and parasites were considered to be common. The Fahrenholz rule stated that parasites generally cospeciate with their hosts. However, this idea is an artifact of the assumptions made and the methods used (Page 2003). The number of rigorously studied parasites with at least some degree of congruent phylogenies is rather small, and none of them is as strictly congruent as the obligate bacterial mutualists of certain invertebrate taxa. A well-studied example is pocket gophers and their chewing lice, where VT and HT are both common (Hafner et al. 1994, Page 2003). Why phylogenetic congruence is seen in this system and not others is still subject to speculation.

6. THE EVOLUTION OF MUTUALISM AND VIRULENCE

To avoid extinction, a symbiont with MMT that loses its opportunities for HT should either evolve benevolence (Fine 1975, Ewald 1987, Bull 1994) or become a reproductive manipulator (Dunn & Smith 2001, Werren et al. 2008). The prediction linking forced exclusive VT to the evolution of reduced virulence has been successfully tested in evolutionary experiments with viruses, bacteria, and algae (reviewed in Sachs et al. 2004) (**Supplemental Table 4*a***). The alternative strategy, the evolution of reproductive manipulation, has, to my knowledge, not been observed during experimentation.

Supplemental Material

The prediction of reduced virulence for VT parasites has led to the transmission-mode-hypothesis, also called the continuum hypothesis, which states that the optimal level of virulence depends on the opportunities for VT and HT (Ewald 1987, 1994; Herre 1995; Kover & Clay 1998; Smith 2007). This hypothesis assumes a continuum with an inverse relationship (trade-off) between VT and HT rates. Optimal virulence is predicted to be positively correlated with the proportion of HT (relative to VT) for lineages within and across species. This prediction was supported in a comparative study of nematodes parasitizing fig wasps (Herre 1995) in which the spatial host population structure (the compartmentalization of fig wasps in figs, where transmission takes place) causes a trade-off between HT and VT across species. Species with one female wasp per fig have only VT and species with on average more wasps per fig also have HT. To explain higher virulence in systems with more HT, Frank (1996b) points to the increased likelihood of multiple infections and, thus, higher within-host competition.

Successfully tested predictions about the evolution of virulence in MMT parasites are, however, largely limited to systems in which experimental (contrasting treatments with exclusive VT

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OPTIMAL VIRULENCE AND THE CONTINUUM HYPOTHESIS

The continuum or transmission-mode hypothesis states that the optimal level of virulence increases with increased opportunities for horizontal transmission (HT). This prediction, however, cannot be generalized because the assumptions made are not widely applicable. Several points that require consideration before predicting the evolution of virulence of MMT parasites emerge.

1. The transmission-mode hypothesis assumes a trade-off between vertical transmission (VT) and HT across systems (different species) or conditions (different environments) without which the optimal level of virulence can hardly be predicted (Lipsitch et al. 1996). However, VT-HT trade-offs are often not found; instead, VT and HT often correlate positively (Kover & Clay 1998, de Roode et al. 2009).
2. The relative opportunities for VT and HT depend on epidemiological dynamics: HT plays a more dominant role during the spread of a symbiont, and more new infections result from VT as prevalence increases (Lipsitch et al. 1995b). At the same time, host population density may be affected as parasites spread, which influences opportunities for HT (Lipsitch et al. 1996, Day & Proulx 2004).
3. The likelihood of multiple infections depends on HT and thus on current epidemiological conditions. As multiple infections drive virulence evolution, virulence becomes strongly dependent on epidemiological conditions (van Baalen 2000).
4. The transmission-mode hypothesis is usually tested on systems in which HT is already associated with virulence. However, even with 100% HT, symbionts may be avirulent or even mutualistic, as with symbionts of lichens, corals, and light-emitting squid and fish.
5. Parasite-induced reductions in host fecundity affect the evolution of VT differently and in more complex ways than parasite-induced host mortality does (van Baalen 2000, Ferdy & Godelle 2005). For MMT symbionts, both forms of virulence play a role. The shape of the trade-off function (if it exists) between virulence and transmission determines whether a single optimal MMT strategy will evolve or a genetic polymorphism with two strategies of predominantly VT or HT will result (Ferdy & Godelle 2005).

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and HT) (**Supplemental Table 4*a***) or ecological (strong spatial population structure, as in the fig wasps) settings determine transmission opportunities (Ebert & Bull 2003). In populations without such constraints on transmission, predictions about the evolution of virulence are much less straightforward and cannot be generalized (Lipsitch et al. 1996) (see sidebar, Optimal Virulence and the Continuum Hypothesis). Thus, the idea that VT is inversely correlated with the optimal virulence of the system is valid only under a restrictive set of conditions that is unlikely in many systems (Ebert & Bull 2003), and the transmission-mode hypothesis is not a general model for the evolution of virulence and mutualism (see the sidebar, Optimal Virulence and the Continuum Hypothesis).

The above discussion shows that it is hardly possible to predict the level of virulence simply from the observation of transmission modes. Avirulence and mutualism have been described in symbionts with exclusively VT, exclusively HT, and MMT (Bright & Bulgheresi 2010). Moreover, a comparative phylogenetic analysis on the origin of mutualism was unable to find support for the hypothesis that VT precedes the origin of mutualism (Sachs et al. 2011). HT in mutualistic partnerships has long puzzled evolutionary biologists because the apparent absence of partner-fidelity feedback makes it difficult to explain how mutualism could be maintained in the face of cheater mutants, which would take the benefits without paying the costs (reviewed in Frank 1996b, Sachs et al. 2004).

7. THE EVOLUTION OF THE MODE OF TRANSMISSION

All things being equal, additional transmission routes are beneficial for symbionts, unless there are costs, such as trade-offs among transmission modes (Mangin et al. 1995). HT and VT have evolved many times independently (Mims 1981, Dunn & Smith 2001, Moran et al. 2008, Sachs et al. 2011). The total loss of HT has also evolved several times independently (Moran et al. 2008, Sachs et al. 2011), whereas the loss of VT is much rarer (Sachs et al. 2011). Among MMT symbionts, rates of VT and HT respond quickly to selection, which suggests that symbionts can evolve rapidly by adjusting their rates of transmission. Experimental evolution studies have generally observed an evolutionary increase in VT in the VT treatments and an evolutionary increase in HT in the HT treatments (**Supplemental Table 4*a***). They have also reported higher symbiont replication rates with higher HT rates.

Supplemental Material

In some systems, the propensity of a symbiont to transmit vertically or horizontally is plastic, with its expression depending on the environment. The key determinant is believed to be the expected reproductive and survival rates of the host. Under conditions of low expected host fecundity and survival, HT is expressed, whereas the opposite is true for the expression of VT (Stewart & Levin 1984, Agnew & Koella 1999, Kaltz & Koella 2003, Refardt & Rainey 2010). In the lambda-phage–*Escherichia coli* system, host stress induces prophage induction and, thus, a switch from VT to HT. This genetic switch can evolve quickly in response to selection and depends on the host's genetic background (Ptashne 2004, Refardt & Rainey 2010). The challenge is to understand the ecological and demographic conditions that favor one or the other mode of transmission.

To date, comparative approaches to identifying these conditions have not led us far. Correlations between mode of transmission and host traits such as life cycles or density have revealed no consistent patterns. For example, the prediction that lysogenic phages, which are vertically transmitted, would dominate in low-density populations (Stewart & Levin 1984) was not upheld in data from aquatic ecosystems (Chibani-Chennoufi et al. 2004). Likewise, there was no clear pattern between the distribution of the microsporidian mode of transmission and various aspects of host biology (Dunn & Smith 2001). These failures are not entirely surprising. The complex epidemiological processes involved in host and symbiont demography are likely to obscure simple correlative patterns (Lipsitch et al. 1995b, Altizer & Augustine 1997, Schinazi 2000). Unfortunately, evolutionary experiments have also yielded inconclusive results. Turner et al. (1998), for example, was unable to support the prediction that increased opportunities for HT in a plasmid infecting *E. coli* would select for an increase in HT. A follow-up study questioned the assumption that high densities of susceptible hosts allow high rates of HT (Turner 2004) and highlighted the difficulties of predicting the evolution of transmission in even apparently simple systems. Magalon et al. (2010) confirmed the prediction that exponentially growing ciliate (*Paramecium*) populations would lead to increased VT of a bacterial symbiont. Interestingly, whereas the plasmid study (Turner et al. 1998) found a trade-off between VT and HT across treatments, the ciliate study (Magalon et al. 2010) found the opposite: Higher VT was associated with higher HT. The difficulties in predicting the evolution of transmission mode were also highlighted in a model (van den Bosch et al. 2010) in which the same set of parameters led to two stable combinations of VT and HT (bistability).

In summary, predictions about the evolution of modes of transmission seem at odds with observed patterns. However, there is no lack of genetic variation for transmission rates. This absence of predictive power may be explained by the high sensitivity of the models to the assumptions made (e.g., the role of trade-offs) and parameters chosen (Lipsitch et al. 1995b, Altizer & Augustine 1997, Schinazi 2000, Ferdy & Godelle 2005, van den Bosch et al. 2010), illustrating the difficulty in predicting the optimal strategy for MMT symbionts.

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8. THE COEVOLUTION OF TRANSMISSION AND SPECIFICITY OF INTERACTIONS

Mutualistic relationships select for reliable transmission from mother to offspring because it is advantageous for both partners. A number of host taxa have evolved highly specialized morphological structures to ensure reliable VT (Buchner 1965, Douglas 1994). In contrast, VT in antagonistic relationships is disadvantageous to the host's offspring (Agrawal 2006, Ebert et al. 2007), and it is in the host's, but not the parasite's, interest to reduce VT. This conflict of interest destabilizes the relationship (Wade 2007). Only parasites that specifically manipulate host reproductive features have evolved the means to stabilize such host-parasite relationships to some degree (Dunn & Smith 2001, Russell et al. 2009).

Above I pointed out that symbionts show ample genetic variation for transmission rates. The same is true for hosts in which variation among host genotypes in the frequency of VT has been observed (**Supplemental Table 4*b***). Taken together, this suggests the possibility of host-parasite coevolution over the rate of VT. Such coevolution was suggested in a study of a microsporidium that infects the planktonic crustacean *Daphnia magna* both transovarially and via waterborne spores. The rate of VT to resting (sexual) eggs was lower to outbred offspring than to offspring from selfed matings (Ebert et al. 2007). Transmission to asexual eggs was 100%. One explanation is that outbreeding renders offspring less suitable for host-genotype-specific adaptations of the parasite and, thus, is adaptive for the host. Host offspring resulting from selfing are genetically more similar to the mother and therefore provide a more familiar environment for the vertically transmitted parasite. That VT is successfully reduced in cases of outbreeding supports the hypothesis that genetic recombination is adaptive in the coevolutionary arms race between hosts and MMT parasites (Agrawal 2006, Ebert et al. 2007) because it hinders virulent parasites from evolving associations specific to the host lineages. Central to this so-called Red Queen hypothesis is that parasites evolve host-genotype-specific adaptations, as has been demonstrated for diverse parasites (Ebert 1998, Packer & Clay 2000, Hatcher et al. 2005, Altermatt et al. 2007). For parasites with MMT, the Red Queen hypothesis relies on two analogous processes: First, genetic recombination breaks up gene complexes in the host genome to which the parasite may have evolved specific adaptations; second, HT breaks up associations of host and symbiont genes. Both of these processes are detrimental to parasites adapted specifically to the host genotype (Hamilton 1980, Agrawal 2006), and together they substantially expand the parameter space under which Red Queen dynamics maintain genetic recombination among hosts (Agrawal 2006).

9. CONCLUSION

In the literature, MMT has been treated primarily as a special case: Most symbionts are treated as either VT or HT. Reviewing the concepts and the available data suggests that MMT symbionts may in fact be the majority class; exclusive VT and HT may both be rare, the latter if we accept that in a social context many symbionts are transmitted from parents to offspring by a physical route often considered to be typical for HT. Considering symbionts as having MMT makes a big difference for their evolution and epidemiology, with examples showing that 100% VT is very different from 99% VT for symbiont evolution (e.g., genome structure) and that 100% HT is very different from 99% HT with regard to epidemiology (e.g., persistence). Further research has to address the theory of MMT to understand the dynamics of these symbionts. Such frameworks need to address not only the epidemiological dynamics of MMT symbionts but also the

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evolutionary processes, such as the dynamics of transmission modes, the possibilities of trade-offs among transmission modes, and symbiont-specific adaptations to the host (see Future Issues below).

SUMMARY POINTS

1. Symbionts with MMT may be the most common type of symbiont on Earth. Exclusive, uniparental VT is rare and seemingly limited to a few obligate mutualistic prokaryotic symbionts of invertebrate host taxa. Other symbionts with predominantly VT are better described as MMT symbionts, even when HT is rare. In contrast, many symbionts with only horizontal physical routes of transmission are often transmitted during social interactions between mothers and their offspring, making these symbionts MMT. Microbiota are also transmitted predominantly by MMT.
2. Transmission events may be so rare that they are not detectable with direct methods. Using multidisciplinary approaches, including population genetics and epidemiology, we can understand the full range of transmission strategies adopted by symbionts.
3. Symbionts with MMT differ in many ways from symbionts with either VT or HT, highlighting that the two modes of transmission combined produce results not readily expected from the sum of their individual effects. This conclusion also applies to symbionts that combine other forms of transmission, such as host-to-host and environmental transmission, sexual and nonsexual HT, and biparental transmission.
4. VT and HT may be traded-off (negatively correlated), but often they are positively correlated. The sign of the correlation is very important for the evolution and epidemiology of the system.
5. Combining two forms of transmission allows symbionts to persist under conditions that would otherwise terminate epidemics or to survive periods when one form of transmission is not possible. Even if VT is rare, it can have a big impact on the overall epidemiology and persistence of the symbiont. In contrast, rare HT makes little difference for the epidemiology, but a big difference for the coevolution of hosts and symbionts.
6. The recognition that MMT is commonplace has far-reaching implications for the treatment of infectious diseases and our understanding of the evolution of virulence and mutualism. For example, MMT may explain the persistence of parasites where models based solely on HT have failed. Control strategies designed for parasites with MMT can offer novel approaches, as reducing or blocking one mode of transmission is often enough to limit the spread.
7. The potential for coevolutionary conflict over the modes and rates of transmission offers exciting avenues for examining unsolved problems in biology, such as the evolution of selfish genetic elements and the evolution of sex.

FUTURE ISSUES

1. If additional modes of transmission are beneficial, why are there so few symbionts with multiple forms of transmission, such as sexual, environmental, vector-borne, maternal, and paternal transmission?

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2. Correlations among rates of transmission modes range from negative to positive and have strong consequences for the biology of a system. Predicting the sign of these correlations would enable a much better understanding of the epidemiology of the system.
3. Symbionts and hosts show ample genetic variation for transmission. What determines the evolution of transmission rates for different modes?
4. A comprehensive theory of the evolution of virulence for parasites with MMT is missing. This theory should not be limited to cases with trade-offs between transmission modes. Such a theory should also address the link between the evolution of virulence and the evolution of transmission modes.
5. VT is beneficial for parasites, but not for hosts. How does this conflict influence coevolution in systems with MMT parasites?
6. Many symbionts, particularly among the microbiota, are transmitted as species assemblages. Multiple levels of selection influence the evolution of such community transmission. What are the drivers of community transmission?

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