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Biology and evolution of sexual transmission

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Sexual reproduction brings together and recombines different genomes. Associated with these contacts is transmission of microorganisms and selfish genetic elements, many of which can be harmful to the host. In organisms with internal fertilization, sexually transmitted infections are caused by pathogens transmitted between the parents participating in mating. Sexual transmission has different epidemiological dynamics from nonsexual transmission in that it is less likely to be dependent on host density, there may be no population density threshold for disease increase, and it is more likely to lead to host extinction. Analysis of the evolutionary pathways that have led to the sexual mode of transmission in pathogens indicates that sexual transmission appears more often to be derived from nonsexual transmission, although the pathways are highly variable, and several groups of pathogens are exceptions to this rule. Sexual transmission has evolved from a wide variety of alternative transmission modes, although rarely from aerially transmitted diseases. More data are needed on the phylogeny and transmission mode of the relatives of sexually transmitted pathogens in order to guide development of animal models and comparative studies.

Keywords: herd immunity; frequency-dependent transmission; phylogeny; disease; infection; transposable elements; uniparental inheritance

Life is a sexually transmitted disease.

R. D. Laing

Introduction

The subject of sex in biology, like in the human sphere, can generate argument, anguish, and strong emotions. Nevertheless, as with people, it may not always be a subject that is free from controversy, or necessarily pleasant, but it is always compelling. In biology, the topic has been studied from numerous perspectives, yet there is still no clear agreement on very fundamental issues such as how sex evolved, what its function is, and what its ramifications are for diverse areas of biology ranging from gene expression, to development, and to evolution.

In biology, there is general agreement that sex is a process that results in the generation of new gene combinations, producing new genotypes by mixing and recombining other preexisting genotypes. It is therefore an efficient method of generating genetic variation that involves the coparticipation (full or partial) of another genome and is distinct from mutation, a process involving changes in the genetic material itself. Just as a recent president could choose his own definition of what sex "is," so a biologist will often choose the term to apply to either the different organisms that come together (male or female), to the process whereby they meet (mating), to the fusion and association of the cells they produce (fertilization), or to their ensuing process of recombination (for example, by meiosis). For example, that meiosis "is" sex is the common view of most population geneticists, if not most presidents.

In prokaryotes, the process of exchange of genetic material is much less ritualized than in eukaryotes that have meiosis. Sometimes it appears disorganized and haphazard, as when multiple viruses infect a cell, and recombination between coinfecting genomes is effected perhaps incidentally by the host's recombination machinery. In bacteria, transmissible plasmids and bacteriophages, themselves

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infectious agents, can incorporate and cotransmit bacterial DNA, and these transmitted fragments can recombine with the genomic DNA of the host. At other times, such as in *Pneumococcus*, there are regular pathways for DNA uptake. While it remains controversial whether their primary function is nutritional or sexual,[1] in either case the outcome is a high rate of recombination between environmentally acquired and bacterial DNA.

In eukaryotes, the process is ritualized, involving a cycle of fusion of haploid cells, a diploid phase of varying duration, and meiosis. The evolutionary pathway whereby this quite universal cycle evolved is unknown; it is almost as if the earth simply shook and meiosis was there. There are no intermediate forms of meioses, and the genes for the meiotic mechanism appear to be present in nearly all eukaryotes.[2] It is a common assumption that meiosis "evolved from" mitosis, but given the universal nature and presumed importance of genetic exchange, the reverse could well be argued; meiosis is unique, but DNA replication is universal. Unfortunately, we have neither phylogenetic nor fossil evidence to settle the issue. It is certainly possible, given the importance of generating genetic variation, to envisage a situation where meiosis evolved before mitosis; however, this is entirely speculative.

Two major hypotheses have been put forward for the evolution of sex and its corollary of genetic recombination. The "repair hypothesis" was first proposed by H.J. Muller, the population geneticist who demonstrated the efficacy of X-rays in producing mutations in *Drosophila*. This hypothesis posits that recombination is there as a repair mechanism to weed out deleterious mutations.[3] This is most easily envisaged if we postulate two haploid organisms that have independently accumulated deleterious mutations. These mutations, if occurring by chance, and at different loci, would be easily purged or "cut out" by recombination, and a defective copy could be replaced by a nondefective viable copy. The process of gradual accumulation of mildly deleterious mutations has been shown to be theoretically likely or even inevitable, especially in small populations, and has been termed *Muller's Ratchet*, and the ensuing result has been given the somewhat panicky name of *mutational meltdown*. Its operation in the world of real organisms has been elegantly described in a book by Graham Bell[4] titled *Sex and Death in Protozoa*. He reanalyzed and reviewed many experiments showing that colonies of microorganisms, if transferred to fresh culture for many years, inevitably lose their vigor, and that this vigor can be "regained" if these colonies are allowed to reproduce sexually. These experimental results both puzzled and intrigued the scientists who first did them, but with no ready explanation at hand, the controversy and interest in them died. In his reanalysis, Bell[4] shows that the data are consistent with the operation of Muller's Ratchet: populations accumulated deleterious mutations, and recombination among different strains resulted in the production of more vigorous offspring.

The second, and perhaps more "optimistic" view, is that sex is there to generate genetic variation and essentially to speed the rate of evolution. This hypothesis requires extreme caution and can become a conceptual quicksand. On the face of it, it seems to argue for an ability of organisms to foresee the future and therefore to foresee a need for evolution, something that they (other than humans) clearly cannot do. There are two ways out of this dilemma, without endangering one's conceptual health. One is to suggest that groups or lineages without sexual reproduction persist for a shorter time than those with sexual reproduction; another is to say that organisms with variable progeny have a higher fitness than organisms that asexually produce progeny identical to themselves. These are not mutually exclusive ideas, and their explicit instantiation and testing by field and comparative studies have now busied evolutionary biologists for more than 30 years.[5,6]

The issue of the advantage of sex becomes excruciating in organisms that are anisogamous (with large "female" and small "male" gametes) or which have differentiated sexes. In such organisms there is what is commonly termed a "two-fold" cost to sex: if females evolve asexuality and produce only female offspring, they would have twice the numerical advantage in terms of offspring number as females that have to produce both males and females. Males do not themselves reproduce, and in the absence of male parental care (a rare phenomenon, of which humans are one of the few examples), all that males do is to provide genetic variance for the offspring. It follows (perhaps oversimplifying somewhat) that for sex to be retained in the face of possible mutations to asexuality, it has to have a two-fold advantage over sexuality. This is not the case in isogamous organisms, where gametes contribute

equal resources to the zygote. Explaining how sex is maintained in anisogamous organisms in the face of the immediate and large disadvantage remains one of the major challenging issues in evolutionary theory. A commonly posited idea is that sex is advantageous in the "arms race" against pathogens that are themselves evolving rapidly.[7] This has been termed the *Red Queen hypothesis* for the advantage of sex, after Lewis Carroll's book, "*Through the Looking-Glass, and What Alice Found There*," in which the Red Queen says, "It takes all the running you can do, to keep in the same place," although the term was first used in biology in the more general context of coevolution.[8]

While sex may have an advantage in providing genetic variation to combat coevolving pathogens, sex also has a major disadvantage in that it also provides a route for the sexual transmission of pathogens. Sex, in all organisms, involves touching, whether this be between genomes, individual cells, or bodies of organisms. Such contact transmits DNA, organelles, and organisms associated with the partners that touch.

We can recognize two types of sexual transmission. One type is "vertical" sexual transmission. In this case, one parent is healthy and the other parent is infected, and the result is that the offspring are infected. Vertically transmitted infectious agents include transposable elements (which can replicate from an "infected" genome onto an uninfected genome), cytoplasmic organelles, and endosymbionts. Vertical sexual transmission can involve a male parent that is infected; in vertical nonsexual transmission, it is usually only females that are involved, and although contacts with males or unrelated individuals may be involved in acquiring the infection originally, the pathways are directly from mother to child and do not involve mating. It is now generally agreed that although transposable elements have sometimes taken on novel and useful functions, for example retrotransposons during the evolution of the immune system and placentation, the majority of active transposable elements are harmful in the short term, and should be considered as genomic parasites. They are rightly sexually transmitted diseases because without sexual contacts new transposable elements cannot spread among individuals in a population (despite spreading within a genome). It was shown theoretically a long time ago[9] that such elements can invade a population even if they cause 50% mortality or sterility of the individuals carrying them. They can therefore, at least potentially, be very serious diseases. Correspondingly, hosts have evolved a large variety of mechanisms for recognizing such genomic and cytoplasmic elements, and inactivating their transcription or limiting their transposition and replication.

The identification and assessment of vertically transmitted sexual infections are not part of the normal everyday business of a clinic involved with sexual health! But biologically transposable elements nevertheless constitute an important component of sexual transmission, with large implications for understanding the evolution of inheritance. An alternative, conceptually useful view of transposable elements is to consider them as having horizontal transmission at the genomic level but bi-parental vertical transmission at the organismal level. Uniparental vertical inheritance at the organismal level (characteristic of chloroplasts and mitochondria) has been argued to be an adaptation to limit or curtail the spread of selfish organelles,[10,11] and by curtailing organelles to one genome achieves the same ends as the "fair" segregation of alleles that occurs at meiosis.

The other more familiar type of sexual transmission is "horizontal," and occurs when a healthy and infected individual meet during mating or sexual contact and the healthy individual potentially becomes infected. When we speak of sexually transmitted diseases in humans, we normally think of this type of sexual transmission; it is with this type of transmission that the rest of the article will be concerned.

> *Diseases are like the stars. The longer you look the more you see.*
>
> Anonymous

Who gets sexually transmitted diseases?

Horizontally sexually transmitted diseases are expected to be confined to particular kinds of organisms.

Firstly, and most obviously, there has to be copulation or some form of mating involving direct contact of the parents, and also probably internal fertilization (although amphibians have contact via amplexus, yet external fertilization). Plants present an unusual case in this regard, as sexual contact is mediated via pollinators carrying pollen from flower

to flower. In this case there can be horizontal sexual transmission via pollinators, and plant sexually transmitted diseases have many features in common with such diseases in animals.[15] Horizontal sexual transmission is also possible without direct contact, as in the case of, for example, viruses that adhere to sperm during external fertilization in fish or viruses that adhere to pollen.[12,13]

Secondly, unless there is an alternative mode of transmission (e.g., via the environment), a sexually transmitted disease requires that the infected organism live across several mating seasons. Thus, a sexually transmitted disease cannot persist in organisms such as many insects that mate only once in a season and then die; this is true even if they have repeated reproduction with many partners within a season. In plants, sexually transmitted diseases are almost entirely confined to perennial species.[14]

Thirdly, species with lifetime monogamy cannot spread disease. However, most species in nature are promiscuous. A substantial number have "seasonal" monogamy, with only one partner during one breeding season but changing partners across seasons. Even fewer have lifetime monogamy, and even this generally does not persist following the death of one partner.

Providing these constraints of internal fertilization and substantial longevity are met, sexually transmitted diseases are ubiquitous. In an earlier review,[15] we identified over 200 diseases in the animal kingdom that were likely to be sexually transmitted. The list was clearly incomplete, and as with all diseases, the number recorded are a function of how well the host has been studied. The correlation between study effort and number of diseases discovered is quite general across plants[16]and animals,[17] including primates.[18] It is no coincidence, for example, that sexually transmitted nematodes of snails were found in France where snails are important gastronomically;[19] or that sexually transmitted fungi have been found on earwigs infesting cabbages in Florida[20] where cabbages are an important crop and earwigs quite off-putting to the shopper; or that sexually transmitted nematodes were discovered in dung beetles in Australia, where such beetles have been introduced and extensively studied in relation to their role in accelerating the decomposition of droppings from cattle and sheep.[15,21] In humans, in the conference brochure, A. Nahmias listed 12 agents that were predominantly sexually transmitted, and another 23 agents in which at least a substantial amount of sexual transmission was involved. Humans seem not untypical of other primates. Thus the World Health Organization[22] lists 11 sexually transmitted diseases out of a total of 96 diseases (ca. 11.5%), while in the primate disease database[23] there are 109 sexually transmitted diseases out of a total of 1,093 (ca. 10.0%).

What are the characteristics of sexually transmitted diseases?

Sexually transmitted diseases have several characteristics that distinguish them from other diseases.[15]

1. They are, almost by definition, diseases of adults. Indeed, an increase in disease incidence following sexual maturity is *prima facie* evidence for sexual transmission.
2. They tend to cause sterility than mortality of the host. There are several, not necessarily mutually exclusive, explanations for the lower mortality and greater sterility caused by sexually transmitted infections. First, the disease associated with sexually transmitted infection is often expressed in the sexual organs, by virtue of these being involved in the contact. Second, sterility may be of adaptive value for transmission of the disease because a failure to conceive, or abortion following conception (as in the case of *Brucella*) may lead to increases in the frequency of mating. Third, it can be shown theoretically that sexually transmitted pathogens and their hosts are more likely to coexist if the disease causes sterility rather than mortality.[15,24]
3. They tend on average to cause less mortality than nonsexually transmitted infections. There are many examples of nonsexually transmitted diseases in humans that are more severe, than their phylogenetically-related sexually transmitted counterparts. For example, meningococcus causes many more severe and fatal diseases than gonococcus, and HSV-1 is also much more severe and fatal than genital HSV-2 when it is transmitted nonsexually, causing both encephalitis and ocular disease. A reason may be that there is a premium on not only keeping the host alive given fewer opportunities for transmission, or as discussed below, their transmission is also dependent on

a healthy sexually active host (in contrast to, for example, vector transmitted diseases, where host incapacitation may favor transmission).

4. They tend to be cryptic, with few overt symptoms. Although difficult to establish for any particular case, this general pattern may have an adaptive evolutionary basis. The assessment of the health of mating partners appears to be a major driving force in the evolution of behaviors associated with mate choice. Thus, birds will often perform cloacal inspection of their partners before mating;[25] in mammals, genital inspection is important in assessing sexual receptivity, but it may also serve to identify infection; and elaborate sexual displays often signal increased host health as has been shown in studies on deer and on barn swallows. Asymptomatic disease expression favors both the host and the pathogen; it is adaptive for the pathogen to remain cryptic and undetected, and adaptive for the partner being "chosen" not to reveal its disease status.
5. They tend to be persistent in the host. In most organisms, mating occurs on a seasonal basis (humans are an interesting exception), and therefore the pathogen needs to persist within the host to the following season if it has no alternative transmission mode. It is therefore also not surprising that many sexually transmitted pathogens cause persistent infections and as such also have numerous mechanisms for evading the immune system.
6. As explained below, their transmission dynamics and epidemiology is likely to be fundamentally different from diseases that have other modes of transmission.

The epidemiology of sexually transmitted infections

Sexually and nonsexually transmitted diseases are likely to differ in terms of how the contact patterns might vary with density. Sexual contacts are likely to be relatively independent of overall population density. At high densities, the number of sexual contacts will be limited by mating opportunity or the length of the breeding season, which is often quite short; by analogy, in humans, a denser dance hall or better attended party does not usually increase the number of sexual partners that an individual has on a particular evening. Conversely, sexual contacts are also unlikely to decrease greatly as population densities decline; the sexual imperative means that organisms are extremely efficient at mate finding even at low densities, and the adaptations for this are legion, for example the elaborate antennae in male moths to detect female pheromones over several kilometers. Again, there are strong analogies with humans, where studies on human population genetic structure showed that marriage distances are much greater in rural areas than in cities;[26] the implication is that partner contact rates are maintained even at low population densities (although such assessments are often based on church marriage records and do not include extramarital contact!). This is in strong contrast to nonsexually transmitted diseases, where high density is frequently associated with higher disease transmission. In humans, this pattern was shown as early as the mid-1800s,[27] and there are other numerous examples in other organisms of increases in disease transmission or disease incidence with increasing density; direct demonstration of this effect via experimental manipulation of densities is frequent.[28,29]

When disease is spread through direct contact, aerially, or via soil or water contamination any increase in the density of hosts is expected to increase the overall level of transmission since susceptible hosts will make more contacts with infected hosts.[30,31] When disease is sexually transmitted or vector transmitted, transmission is generally thought to be more likely to be frequency dependent.[32–34] Under this assumption, a host's number of contacts is expected to stay relatively constant despite any changes in population density, as individuals will have a fixed number of sexual contacts and vectors will search for a fixed number of hosts. An important implication of this is that when transmission is frequency dependent, it is possible for the parasite to drive the host population to extinction because the transmission rate does not drop towards zero as the population density decreases, as is the case when transmission is density dependent.[32] In addition there is no critical community size, and hence no herd immunity, for the persistence of diseases with frequency-dependent transmission.[32]

Evolution in diseases with frequency-dependent transmission

Classical theory on the evolution of pathogen virulence assumes that the number of secondary cases

due to a single infected individual (the epidemiologically defined R_0) is maximized.[35] When there is no constraint between transmission and virulence, we therefore predict the evolution of maximal transmission and minimal virulence. Boots and Sasaki[36] showed that if a disease with frequency-dependent transmission can increase transmissibility without increasing the host mortality (or even if this dependence is weak), it will often evolve to wipe out its host and, therefore, itself. In contrast, when the transmission of the parasite is density dependent, the evolution of maximal transmission will tend to cause instability in the host population dynamics, and such population instability will often lead to the stochastic fade out of the pathogen, resulting in a disease-free host population. Virulence is often thought to be a by-product of transmission as an increased production of infective stages may damage host tissues[37,38] and therefore, in reality, increased transmission may not be bought without a substantial cost in terms of virulence.[39] Boots and Sasaki[36] showed that a finite virulence and transmission only evolves where higher transmission becomes increasingly costly in terms of increased virulence (a "saturating" relationship). Without this relationship, we will again tend to get the evolution to parasite driven host extinction. It may therefore be a prediction that the persisting sexually transmitted diseases seen in nature will tend to show this form of constraint, but this has never been empirically tested. Even when we do have this saturating relationship, there is still the possibility of the evolution to extinction as the finite evolutionarily stable transmission rate may lie within the extinction region. Therefore, independent of the form of the relationship between transmission and virulence, there is always the possibility of evolution to extinction when transmission is frequency dependent. The implication of this is that if sexually transmitted diseases do have frequency-dependent transmission, there is the possibility that they may evolve to cause host extinctions. This is a frightening thought; for example, imagine the population consequences of a disease such as AIDS in the absence of any available therapy or consciousness about its transmission mode.

Experimental tests of the theory

Given the important implications of frequency dependent rather than density-dependent transmission, there have been remarkably few experimental tests of many aspects of this theory. This is due to a lack of appropriate experimental systems, although there is one insect and one plant system that have been used to examine the theory. Ryder *et al.*[40] used the two-spot ladybird, *Adalia bipunctata*, and its sexually transmitted parasitic mite, *Coccipolipus hippodamiae* to carry out an experimental test of the frequency-dependence assumption. This system provided an excellent model because extensive prior field and laboratory studies of the system's dynamics allowed the design of realistic experiments. They manipulated both the density and frequency (= prevalence) of infectious ladybirds within enclosed mating arenas. The key result was that transmission of the mite in the two-spot ladybird depended more on the density of infected individuals in the study population than on their frequency. In this system, therefore, sexual contact rate was affected by density, but much more research is needed to establish if this is generally true in other animals. Population dynamics of such sexually transmitted infections may therefore exhibit characteristics of diseases with density-dependent transmission.

Refinements of the theory

Ryder *et al.*[34] followed up the results of their experiment with a theoretical study that refined the transmission functions in the light of their results. In particular, they assumed that the transmission of infection often occurs through more than one type of contact, each of which may have a different functional relationship with population density. Various factors at the level of individual behavior may give rise to such dynamics.[41,42] For example, sexually transmitted diseases may sometimes be transmitted partly through social contacts,[43,44] resulting in a component of density-dependent transmission, because social contacts will often be density dependent. A similar argument can be applied to ordinary nonsexually transmitted diseases. For example, most aerially or direct contact transmitted infections may commonly be transmitted during sexual activity, leading to a component of frequency-dependent transmission.[45] Ryder *et al.*[34] analyzed a novel form of transmission function that allows for combined density and frequency dependence. They showed that introducing even a small component of frequency dependence can lead to parasite-driven extinction, while the introduction of density-dependent transmission generates

threshold dynamics in an otherwise frequency-dependent model.[34] Therefore, even more general and arguably more realistic assumptions about transmission dynamics still predict extinctions due to STIs.

This classic infectious disease theory assumes that transmission depends on population wide densities or frequencies of the parasite. However, transmission is fundamentally a local process between individuals that is determined by their behavior (and/or that of a vector). Best *et al.*[46] recently examined the implications of local transmission processes to the likelihood of disease driven host extinction and showed that although local density-dependent transmission can lead to parasite driven extinction, extinction is (as in the population-wide or global case) more likely under local frequency-dependent transmission and much more likely when there is active local searching behavior for mates.[46] This work emphasizes that local processes are essential in determining parasite driven extinctions, and the role of parasites in the extinction of rare species may have been underplayed due to the classic assumption of global density-dependent transmission.

Population genetics and quantitative genetics of sexual transmission

Microorganisms have a very large variety of transmission routes. Thus, they can be environmentally transmitted through the soil, water, air, or via fomites; they may be vector transmitted; or they may be transmitted by direct contact, including sexual contact. Quite diverse transmission modes can occur in closely related pathogens, suggesting that evolution of novel transmission routes may be commonplace in nature. However, for most microorganisms we know neither the evolutionary pathways that these transmission modes have taken, nor the evolutionary forces that have been responsible for their direction.

Very few pathogens have only one transmission mode; many sexually transmitted pathogens are also transmitted vertically or by close contact, and even what we think of as nonsexually transmitted diseases such as influenza are no doubt often transmitted during the close contact associated with sexual activity. This has led to the classification of diseases as being due primarily to sexual transmission (STIs), or diseases where sexual transmission plays a large role (STxIs) but that primarily use other transmission modes (Nahmias, this volume). In humans, an increase in sexual activity involving oral–genital or oral–anal contact has led to a corresponding increase in the prevalence of these diseases.

Sometimes it is not clear if a given transmission mode has evolved at all or is simply the product of the ecology of the host and unrelated to evolutionary change in the pathogen. For example, an increase in partner exchange rates may allow a pathogen that otherwise is transmitted by nonsexual contact to spread and sustain itself in a population by sexual contacts. It has been suggested that many of the common, highly infectious childhood diseases that result in lifetime immunity are a "product" of civilization in that they require large populations for their spread and persistence in the face of epidemic fadeout.[47] Perhaps the spread of these diseases did not necessitate any genetic changes whatsoever in transmission mode or even transmission rate. Similarly, it has been argued that HIV might have been a relatively minor disease, but for the increased interconnectedness of villages in Africa, and its subsequent spread to subgroups with high levels of sexual activity and partner exchange.[48] Behavioral changes in sexual activity (brought about, for example, by the ready availability of the pill), changes in movement patterns, and internationalization, have all changed the dynamics of human infectious diseases and such changes have occurred in a time span of less than a generation.

It is nonetheless likely that in most systems, transmission modes are genetically determined; it is well known that particular pathogen strains of, for example, genital and *Chlamydia trachomatis* are associated with particular tissue tropisms and particular transmission modes.[49] We have very little data on the level of genetic variation in transmission mode within most species, undoubtedly due to the difficulty of determining actual transmission routes of pathogen variants, whether in natural animal or human populations.

It would be obviously advantageous for any pathogen to use all possible transmission routes, yet there are likely to be trade-offs between these routes, as in any evolutionary process involving a complex phenotype. In an evolutionary context, trade-offs are quantified by measuring the genetic correlations between different traits, and if there is a negative genetic correlation between alternative transmission modes, this would suggest that increasing one

transmission mode would result in a decrease in another transmission mode. Remarkably, no studies appear to have tried to measure if such trade-offs in transmission mode exist in extant pathogens. However, the circumstantial evidence that such trade-offs exist and have a genetic basis is strong. Contrasting transmission modes occur in closely related taxa. Many sexually transmitted diseases show an interesting, contrasting duality with both sexual and nonsexual transmission being found in closely related strains.[41] However, it is difficult to extend this qualitative pattern into a more rigorous quantitative theory of transmission mode evolution. Moreover, at least in humans, the transmission mode is usually inferred from tissue tropism rather than direct observation; therefore it is hard to gain a quantitative sense of the process in any particular system.

As discussed above, there are likely to be contrasting relationships between population density and transmission in sexually and nonsexually transmitted diseases. Sexual transmission would be favored in host populations at low density, and nonsexual transmission in populations at high density. There may exist some density at which both transmission modes contribute equally to transmission[42] (the "social-sexual crossover point"). While evolution may favor one transmission mode relative to another depending on the population density, the situation is more complicated in that the presence of the disease, by increasing the mortality or decreasing the fertility of infected hosts, can itself affect population density. It can be shown that if the effects of the nonsexually transmitted infection are such that it reduces the population density to below the social-sexual crossover point, then genes determining sexual transmission can invade; conversely, if the effects of the sexually transmitted disease are such that the population at equilibrium would be above the social-sexual crossover point, then genes determining nonsexual transmission can increase in frequency. Under these conditions, it is possible to maintain a genetic polymorphism, with both types of transmission persisting in the same population.[41] Such stable coexistence of sexually and nonsexually transmitted strains can occur even if they exclude each other immunologically from the same individual host; the example provides an interesting exception to the famous Gause's Law in ecology, which states that two organisms that use the same resource cannot coexist in one population. Clearly, such a law only considered the issue of competitive exclusion in the context of access to resources, whereas in a host–pathogen system there is differential access by sexual and nonsexually transmitted pathogens to host resources depending on the host density. Given this theory, it is therefore not surprising that in many human pathogens both sexual and nonsexually transmitted strains cooccur in the same populations (see the next section for examples). But there is an important qualification: while this is a cogent explanation, data to parameterize and test the application of such models to real populations have not been obtained in any organism. It could well be that many other processes are responsible for the cooccurrence of different strains (e.g., heterogeneity in contact rates, interpopulation migration, transient evolution between one state and another).

Evolution of sexual transmission

It is unknown if the trait of sexual transmission has reevolved across the parasitic tree of life frequently or rarely. Some expectations can be posited, but they are rather contradictory. On the one hand, there are reasons for thinking that sexually transmitted diseases may be ancient. Because their transmission is likely to be relatively independent of host density, sexually transmitted pathogens can be maintained in small populations. If a speciation event or some catastrophe has resulted in population bottlenecks, then sexually transmitted pathogens are less likely to be lost than pathogens that require large populations for their persistence. Moreover, because sexually transmitted pathogens are often immunoevasive and generally have quite low rates of increase, their dynamics tend to be endemic rather than epidemic. Sexually transmitted diseases are therefore much less likely to show "fade-out" than highly infectious aerially transmitted diseases such as flu or measles that induce strong immune responses. Their long infectious period also increases the chance that they will be carried with the host if it colonizes a new area. Also, because mating and sexual reproduction are relatively constant features of a species (unlike, say vector occurrence, which may be highly dependent on weather conditions) the transmission mode would seem to be a "reliable" one over the long term.

On the other hand, sexually transmitted pathogens are almost by definition in a strong "cul-de-sac;" mating typically only occurs within

a species, and hence the opportunities for cross-species transmission are reduced or even nonexistent. Indeed sexually transmitted pathogens have significantly lower host ranges than nonsexually transmitted pathogens.[15] Sexually transmitted pathogens are therefore less likely to expand onto other host species, a factor that could be absolutely critical for long-term persistence if a host species should go extinct. There are several possible pathways that might lead to the presence of sexual transmission in a pathogen on a particular host. Sexual transmission may arise by cospeciation or as a host shift of a pathogen that is already sexually transmitted; the latter is unlikely when cross-species mating is rare. Alternatively, the pathogen may evolve sexual from nonsexual transmission, either on the same host or directly following a host shift.

In order to investigate this, we reviewed studies on the phylogenetic relationships of pathogen groups that had representative species or strains that were sexually transmitted. By mapping transmission mode onto a phylogeny of the pathogen and its relatives, it is possible to infer, in theory at least, whether within a particular group, sexual transmission in extant present day pathogens came from ancestors that were themselves sexually transmitted (i.e., sexual transmission is an "ancestral" trait in the pathogen), or if sexual transmission evolved from pathogens that had nonsexual transmission (in which case sexual transmission is considered a "derived" trait). One of the strengths of phylogenetic analysis is that character trait changes can be studied across that phylogeny if the genetic markers used to construct the phylogeny, such as DNA sequence data, can be considered to be evolutionarily uncorrelated (or weakly so) with the characters being investigated. In general, the process uses some form of model-fitting based on likelihood or parsimony to determine the minimum number of evolutionary changes that best explain the distribution of the trait in present day populations. While straightforward in principle, it requires an accurate phylogenetic tree topology, a very complete phylogeny, and accurate determination of the trait status in all of the taxa in the phylogeny. Not only do the phylogenetic relationships of the different lineages need to be determined with high confidence, but also the transmission modes in these lineages needs to be accurately determined. In our analyses, absence of accurate information on the transmission mode of the various pathogens was a greater obstacle to interpretation than accurate phylogenies (see below). These criteria are difficult to meet with any confidence. It is unlikely that any collection of taxa is complete and that there has not been taxon extinction. This would not matter if the extinction/speciation was random with regard to the trait being mapped, but as discussed above, transmission mode may well be correlated with lineage extinction or branching onto new hosts, but the directions in which this might work are hard to predict.

While we used well-defined sexually transmitted pathogens as focal species in the phylogenies, accurate determination of the transmission mode of the relatives of these pathogens was often a serious limitation in the analysis. When these relatives did not cause overt disease or were present in wild species, there was almost never a very precise description of the transmission mode; for example, many SIVs in wild primates were described as being transmitted "probably by biting between males, and sexually between males and females" with little available data to support these conjectures.[50,51] Often their "transmission mode" had to be inferred from the site of isolation of the strain (in HPV, cutaneous vs. genital; in *Chlamydia* often ocular vs. urinogenital) rather than any epidemiological evaluation of the precise transmission route. Computer packages are available for mapping traits onto phylogenies algorithmically but in nearly all cases, because of the inadequate quantification of transmission mode, we found that the inferences, if they could be made at all, were best made qualitatively and by careful inspection of the actual data and associated literature.

To investigate the evolutionary relationships of lineages of pathogens with sexual transmission and with nonsexual transmission, we used the pathogens causing sexually transmitted diseases listed in Lockhart *et al.*[15] restricting our search to sexually transmitted diseases in mammals, for which the best information is available (see Appendix S1). Out of 40 pathogens in which sexual transmission was recorded as "common and important" (a sexual transmission score of 3 or above in Lockhart *et al.*[15]), usable phylogenetic information was available for 32 of them. Some phylogenies were excluded from consideration because there was weak sampling of related taxa, related taxa were very distant phylogenetically, or the available phylogenetic trees were unrooted with no outgroup. With

the advent of high throughput sequencing of the microbiome of many organisms, it is likely that we will have much more complete phylogenies in the future; for example, recent studies of *Chlamydia* infection in Koala bears has revealed numerous hitherto undetected strains of *Chlamydia*-like organisms.[52]

The results (Table 1) show that it seems far more common for sexual transmission to be a derived trait rather than an ancestral trait. Among these examples, sexual transmission appears to have evolved in an extremely diverse, one might even say, bizarre way. Canine transmissible venereal tumor in dogs is a highly metastatic cell line derived from the host itself; remarkably, quite independently, a similar host-derived transmissible tumor has recently been found in the Tasmanian devil, a marsupial where transmission may be also sexual but is often ascribed to biting that is part of the intra- and intersexual contacts during mating. Dourine is a sexually transmitted disease in horses caused by trypanosomes. Surprisingly, dourine appears to be caused by trypanosomes closely related to trypanosomes transmitted by tsetse flies and causing sleeping sickness in humans and with reservoirs in other large mammals (*Trypanosoma brucei*); there is no consistent or identifiable sequence divergence between the isolates causing dourine and those causing sleeping sickness, suggesting that the cross species transmission event plus acquisition of a new transmission mode may not have involved or required any evolutionary changes. In other cases, sexual transmission appears to have evolved from intestinal pathogens and commensals that are often fecal/orally transmission (e.g., campylobacter) or from direct contact transmission (e.g., syphilis).

In only some pathogen lineages did sexual transmission appear to be the ancestral state, and then usually in those lineages where there were also alternative transmission modes and where the relative contribution of the sexual route to overall transmission was only moderate. Sexual transmission was characteristic of many of the alpha herpesviruses, chlamydias, brucellas, and SIVs/HIVs and STLVs/HLTVs. In several of these lineages, nonsexual transmission appeared to be derived from sexual transmission, as in the case of HSV-1, *Brucella melitensis* and *Brucella abortus*. In other groups, such as the chlamydias and HPVs, there were multiple lineages, some of which seemed to be sexually transmitted while others were nonsexually transmitted. Alternative transmission modes often require precise tissue tropisms. It was sometimes difficult to tell (without additional information) whether the strain was able to infect both tissue types without any evolutionary/genetic change or whether a change in transmission had been contingent on a genetic change (what we would call evolution of a new transmission mode). Two features help clarify this. First, if a specific genetic pathway that determines a specific tissue tropism has also changed then it is very likely that a genetic change was involved (as the case in *Chlamydia*). Second, if a distinct lineage consistently has a particular transmission mode among all the branches within that lineage then it is likely that its tissue specificity is genetically determined (as was the case with some HPV types). Within the chlamydias and HPVs, in some strains sexual transmission appeared to be a derived trait, while in other strains it appeared to be ancestral suggesting frequent "evolutionary switching" between the two modes; however, it was not always possible to be confident that the presence of these pathogens in alternative tissue types was related to any genetic change.

Moreover, it would be of interest (and medical relevance) to know if the evolution of these tissue tropisms is facilitated by repeated mutation (perhaps having a simple genetic basis), or if they are being transferred among strains by recombination (in the case of viruses) or by plasmid transfer (in the case of bacteria).

It would seem that even though sexually transmitted pathogens might be expected to be persistent within a species and, given the regularity of sexual contacts, perhaps even be "enduring" at an ecological level, our data suggest that they may not persist in the longer term. The greater persistence of pathogen lineages with nonsexual transmission may simply be because they have a greater chance of transmission to other species. In the pathogen groups with persistent sexual transmission, alternative transmission modes are often present. More generally, it is unclear how "evolutionarily flexible" transmission mode might be, and this would be important to know especially in the era of vaccines with incomplete strain coverage. Regrettably, far more studies have focused on the evolution of virulence in pathogens than on evolution of transmission mode. Several sexually transmitted diseases have originated within historical times (e.g., syphilis, dourine, HIV),

Table 1. Evolutionary origin of sexual transmission in mammalian and human pathogens[a]

Pathogen/Parasite	Host	Common name	Score	Sexual transmission origin
Poxvirus MOCV	Homo sapiens	Molluscum contagiosum	3.5	?ancestral
HIV-1	Homo sapiens	AIDS	5	?ancestral
HIV-2	Homo sapiens	AIDS	5	?derived
HPV	Homo sapiens	Genital warts, papilloma virus	5.5	derived and ancestral
HSV-2	Homo sapiens	Genital herpes	4.5	ancestral
HTLV-1	Homo sapiens	Adult T cell leukemia	3	ancestral
HTLV-2	Homo sapiens	Adult T cell leukemia	3	?ancestral
Klebsiella granulomatis (=Calymmatobacterium granulomatis)	Homo sapiens	Granuloma inguinale (donovanosis)	5	derived
Neisseria gonorrhoeae	Homo sapiens	Gonorrhea	5.5	derived
Gardnerella vaginalis	Homo sapiens	Vaginitis	4	?derived
Hemophilus ducreyi	Homo sapiens	Chancroid	6	derived
Chlamydia trachomatis	Homo sapiens	Chlamydia	5.5	switching
Neisseria gonorrhoeae	Homo sapiens	Gonorrhea	5.5	derived
Treponema pallidum	Homo sapiens	Syphilis	6	derived
Trichomonas vaginalis	Homo sapiens	Trichomoniasis	5	?derived
Phthirus pubis	Homo sapiens	Pubic lice	5	? derived
Sarcoptes scabia	Homo sapiens	Scabies	4	? derived
Simian agent 8	Papio spp.	Simian herpes (agent 8)	5	ancestral
SIV	Cercocebus atys	Simian immunodeficiecy virus	5	ancestral
BHV-1	Bos taurus	Bovine coital exanthema	6	? switching
Parapoxvirus	Ovis aries	Venereal orf	3	ancestral
Parapoxvirus	Capra hircus	Venereal orf	3	ancestral
Brucella canis	Canis familiaris	Canine brucellosis	4	derived
Brucella ovis	Ovis ares	Brucellosis	4	?ancestral
Campylobacter fetus	Bos taurus	Bovine genital campylobacterosis	6	derived
Chlamydia psittaci (= pecorum)	Phascolarctos cinereus	Koala herpes	4	switching
Taylorella equigenitalis (= hemophilus)	Equus caballus	Contagious equine metritis	6	derived
Treponema paraluis-cuniculi	Leporidae	Rabbit syphilis	4	?derived
Trypanosoma equiperdrum	Equus caballus	Dourine	5.5	derived
Ureoplasma spp.	Ovis aries	Sheep ureoplasma	6	switching
Trichomonas foetus	Bos taurus	Bovine trichomoniasis	6	?derived
Canis familiaris—cell line	Canis familiaris	Canine venereal tumor	5	derived

[a]Score is the degree of sexual transmission as estimated by Lockhart *et al.*[15], where 6 = "always," 5 = "in almost all cases," 4 = "usually," and 3 = "common and important." For references and full table, see Appendix S1. Question mark indicates that the conclusion about origins is tentative and not strongly supported. No usable phylogeny or insufficient information on transmission was found for the following: EHV-3, equine coital exanthema; CHV-1, canine herpes; CpHV-1, caprine herpes; HSBV, herpes simian B virus; Klebsiella aerogenes, horse endometritis; Pseudomonoas aeruginosa, horse pseudomonas; Proteus mirabilis, bacterial infection; Salmonella abortus ovis, ovine salmonella.

and shifts back to nonsexual transmission (e.g., in the caprine brucellas and HSV-1) might be relatively recent and related to increased density of animal and human populations associated with civilization.

Conclusions

Sexual contact and hence sexual transmission of disease is ubiquitous, in both prokaryotes and eukaryotes. Sexual contact is essential for the transmission of genomic parasites. Transposable elements are sexually transmitted genomic parasites that potentially could be highly lethal or sterilizing and still spread. The fundamental epidemiology of sexually transmitted diseases is likely to be different from other directly transmitted diseases. The rate of disease spread is less dependent on host density and there is no threshold density of susceptible individuals for disease increase; the concept of "herd-immunity" therefore does not apply. Sexual transmission provides a short-term assurance strategy for pathogens that otherwise require large population sizes to persist. This has important implications for implementation of vaccination policies and for disease eradication. The understanding of the phylogenetic relationships of sexually transmitted pathogens and commensals is in its infancy, as is our understanding of the evolutionary pathways and forces that lead to different transmission modes. Understanding these phylogenetic relationships provides a rational basis for choice of animal models for the study of disease, it provides a basis for comparative studies of disease pathology, and it is important in forming expectations about the nature of future disease emergence.

Supporting information

Additional supporting information may be found in the online version of this article.

Appendix S1. References and data for Table 1.

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Conflicts of interest

The authors declare no conflicts of interest.

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