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Genetic bottlenecks in intraspecies virus transmission

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Abstract

Ultimately, viral evolution is a consequence of mutations that arise within and spread between infected hosts. The transmission bottleneck determines how much of the viral diversity generated in one host passes to another during transmission. It therefore plays a vital role in linking within-host processes to larger evolutionary trends. Although many studies suggest that transmission severely restricts the amount of genetic diversity that passes between individuals, there are important exceptions to this rule. In many cases, the factors that determine the size of the transmission bottleneck are only beginning to be understood. Here, we review how transmission bottlenecks are measured, how they arise, and their consequences for viral evolution.

Keywords

virus; bottleneck; transmission; diversity; evolution

Main Text

Many viral pathogens exist as diverse populations within infected hosts. The diversity present in this “mutant swarm” provides the raw material on which selection can act. Although populations within a host may reach as high as 10^{14} virions [1], viruses are frequently subject to bottleneck events as they spread within and between hosts [2]. These bottlenecks drastically reduce the size of the population and, consequently, its genetic diversity. Because the population that develops after a genetic bottleneck is derived from a small sample of the ancestral population, this process can dramatically alter the relative frequency of mutations in the population.

The stringency of the transmission bottleneck plays an important role in linking within-host processes to a pathogen’s larger evolutionary dynamics. Stringent, or tight, transmission bottlenecks limit the diversity of the founding population in the recipient and alter the

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mutational composition of the population in the recipient relative to that in the donor (Figure 1, top). However, if the transmission bottleneck is loose, transmission does not significantly impact variant frequencies and the composition of the founding population in the recipient more closely matches that present in the donor at the time of transmission (Figure 1, bottom).

Although transmission bottlenecks play an important role in viral evolution, relatively little is known about their size and determinants. Many quantitative studies suggest that bottlenecks are tight [3,4]; however, there are exceptions and even conflicting reports for viruses with similar transmission pathways. Importantly, the factors that determine the stringency of the transmission bottleneck are poorly understood. Here, we briefly review how transmission bottlenecks are measured, how they arise, and their impact on viral evolution across biological scales. For a more comprehensive review of bottlenecks, including those found at the within-host and cellular scale, we direct the reader to reference [3].

Measuring transmission bottlenecks

Transmission bottlenecks are measured by their effect on viral diversity. In experimental systems, within-host diversity can be approximated using a defined population of viruses that are tagged with genetic markers. If the markers are selectively neutral, the number of distinct markers that pass from donor to recipient reflects the sampling event of the bottleneck as opposed to selection within either host (Figure 2A). This technique has been used to qualitatively estimate a stringent bottleneck for aphid transmission of cucumber mosaic virus (an average of 3 of 12 markers were transmitted) [5] and aerosol transmission of influenza in ferrets and guinea pigs (2–5 of 100 sequence tags were transmitted) [6**]. In a particularly elegant experiment, Moury and colleagues artificially inoculated aphid vectors with mixtures of 2 Potato Y virus mutants prior to feeding the aphids on pepper plants [7*]. By modeling the number of plants exposed to only one of the mutants, Moury *et al.* found that aphid transmission imposes a bottleneck of 0.5–3.2 virions on Potato Y virus.

Because natural systems do not offer the opportunity for a barcoding approach, early studies characterized the transmission bottleneck qualitatively based on the degree of shared diversity found within transmission pairs (Figure 2B). Clonal sequencing of influenza virus isolates from swine and equine transmission chains found transmission pairs shared minority variants [8–10]. Studies of aphid, mechanical, and vertical transmission of Zucchini Yellow Mosaic Virus found similar results [11,12]. These studies suggest that transmission bottlenecks are sometimes sufficiently loose to allow for the transmission of low-frequency mutations.

More quantitative approaches can also be employed to estimate the transmission bottleneck from shared diversity data. In these models, the transmission process is assumed to be a random sampling of the donor population and individual variants are assumed to be transmitted independently of one another. The probability that a variant is transmitted is derived from a binomial distribution and is positively correlated with its frequency in the donor and the size of the bottleneck. More complexity can be incorporated into these models to tease apart the relative impact of within- and between-host processes (see ref [13**] for a

thorough discussion and comparison of common models). One such model has been used to estimate a loose bottleneck of roughly 200 genomes in a recent study of human transmission of influenza virus [13**,14]. This estimate is much larger than that provided by the barcode experiments previously discussed. The large discrepancy in these studies highlights the need for a more complete understanding of the viral, host, and environmental factors that determine transmission bottleneck sizes.

When only one member of a transmission pair is available, the diversity present in the infected host can be used to estimate the number of genotypes in the founding population. Coalescent theory works backward in time, tracing the evolutionary history of the current population back to common ancestors [15]. Coalescent models based on the current diversity, the viral evolutionary rate, and the estimated time of infection can be used to determine how many genotypes were present in the founding population (Figure 2C). Phylogenetic analysis of HIV evolution suggests that most infections derive from small founding populations of only one genotype [16,17]. A similar approach has been used to estimate a stringent transmission bottleneck for HCV [18*–21].

Determinants of bottleneck size

Most transmission studies suggest tight bottlenecks and small founding populations (see tables in [3] and [4]). However, as mentioned above, these estimates can vary significantly depending on the virus, host, route of transmission, and experimental design. Understanding the factors that determine the size of the transmission bottleneck is vital to interpreting the effect transmission has on viral evolution. Work in Tobacco etch virus (TEV) suggests that the size of the bottleneck is dose dependent, with higher exposure doses corresponding to larger founding populations [22]. Evidence from mixed infections of influenza virus in a guinea pig model is consistent with a dose dependence model [23]. Further support comes from experimental infections with tagged influenza clones in ferret and guinea pig models, which indicate that the more limiting exposure dose of aerosol transmission imposes a significantly more stringent bottleneck than contact transmission [6**]. Additionally, coinfection by other pathogens, which can limit innate defenses and modulate the immune response, has been correlated with loose bottlenecks in HIV and HCV [24,25,26]. Taken together these data suggest that the transmission bottleneck is not constant, but rather a complex function of both viral and host factors.

Complicating matters is the observation that segregation of the viral population within the donor can also restrict the amount of diversity transmitted to the recipient. Work in animal models of influenza virus suggest that populations in the upper respiratory tract seed transmission and can be distinct from populations at other sites of infection [6**,27]. The stringent bottleneck associated with aphid transmission of cucumber mosaic virus [28] is likely the result of extreme viral segregation within the donor. Most plant cells are infected by only one genotype, and aphids are unlikely to feed on many donor cells prior to transmission [29]. Other vector-transmitted viruses undergo an additional bottlenecking event within the vector. Smith *et al.* used fluorescent Venezuelan equine encephalitis virus (VEEV) replicons to show that an average of 28 midgut cells in the mosquito are initially infected by the virus [30]. This small population size is consistent with observations of

Dengue virus in infected mosquitos [31] and likely contributes to the stringent bottleneck observed during mosquito-mediated transmission of VEEV in a mouse model [32*].

To this point we have focused on stochastic bottlenecks that randomly sample the donor host population during transmission. In some cases, however, selection within the donor and/or recipient hosts can impose selective sweeps that decrease the diversity of founding populations. While HIV-infected individuals can harbor highly diverse viral populations, phylogenetic approaches indicate that often only one donor genotype contributes to founding the recipient population [17,33]. This trend is often observed even when physical barriers to infection are bypassed, as is the case among intravenous drug users [34,35]. Comparisons between the populations present in the donor genital tract and recipient blood stream suggest that minor variants in the genital tract are preferentially transmitted [36**]. This biased transmission implies that the bottleneck event is not a random sample of the donor population. Larger cohort studies have shown that transmitted viruses are most similar to those present early in the donor infection [37] and are better suited to spread between hosts [38*]. Transmitted viruses are characterized by CCR5 receptor preference [39–42], lower levels of glycosylation on the surface envelope protein [43,44], and lower susceptibility to type 1 IFN [45,46*] than the majority of variants present in chronically infected hosts. Taken together, these data suggest that selective pressures in naïve hosts impact the stringency of the HIV transmission bottleneck. For more detailed reviews of HIV transmission, we direct the reader to references [33,47,48].

Evolutionary consequences of transmission bottlenecks

Transmission bottlenecks determine the extent to which within-host diversity contributes to evolutionary trends at higher scales. While the relatively high mutation rates and large population sizes of many viruses may allow these pathogens to rapidly adapt to their host, the rate of adaptation is not unlimited. In particular, the rate depends on the effective population size [49*]. The effective population size can be roughly thought of as the number of viruses that replicate and contribute genomes to the next generation. It is usually smaller than the census population (see [50] for a thorough review and discussion of effective population size). In large effective populations, selection is efficient, deleterious mutations are purged, and beneficial mutations steadily increase in frequency over time [51]. However, alleles in small populations are subject to sampling error known as random genetic drift. Drift introduces noise so that selection does not efficiently fix beneficial mutations or purge deleterious ones [52]. Stringent transmission bottlenecks reduce the effective population size of viral pathogens between hosts, increase genetic drift, and decrease the efficiency of selection.

Stringent transmission bottlenecks may therefore pose a significant barrier to adaptive evolution. Because most mutations are deleterious, repeated bottleneck events fix deleterious mutations and decrease viral fitness over time. This process, known as Muller’s ratchet, opposes purifying selection and contributes to the deleterious load often observed at the tips of viral phylogenetic trees [53,54]. Although the fixation of deleterious mutations decreases fitness along a single transmission chain, it is unlikely to drastically decrease a virus’ overall fitness at a global scale. Competition at the interhost level, can serve to maintain viral fitness

[55,56*]. Notably, populations with low fitness are not as susceptible to Muller's ratchet as well-adapted populations with high fitness [57,58]. We speculate that the fixation of deleterious mutations during transmission is less likely to affect the evolution of recently emerged viruses, which might have lower fitness in their new host species. However, emerging viruses face an alternative problem as stochastic bottlenecks may purge beneficial mutations before they reach fixation.

While transmission bottlenecks are expected to slow adaptive evolution, they may provide potential advantages to evolving pathogens. Stringent bottlenecks purge the population of defective interfering particles, which limit viral replication [59]. Bottlenecks also increase genetic drift and provide a mechanism for virus populations to traverse potential fitness valleys and escape local fitness maxima [60].

Concluding thoughts

The available data suggest that transmission frequently imposes a stringent bottleneck that dramatically reduces the level of diversity in the founding population. In many cases, however, transmission bottlenecks appear to be sufficiently wide to transmit minority variants. Defining the host and viral factors that determine the transmission bottleneck is an important step in developing strategies to limit viral transmission. A more complete understanding of viral transmission bottlenecks is also necessary to link within-host population dynamics to larger evolutionary trends.

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Highlights

- Bottlenecks restrict the transmission of genetic diversity between hosts
- A variety of methods can be used to estimate bottleneck size in experimental and natural infections
- Some bottlenecks are selective, but most appear to be stochastic in nature
- Bottlenecks link within host processes to larger evolutionary dynamics

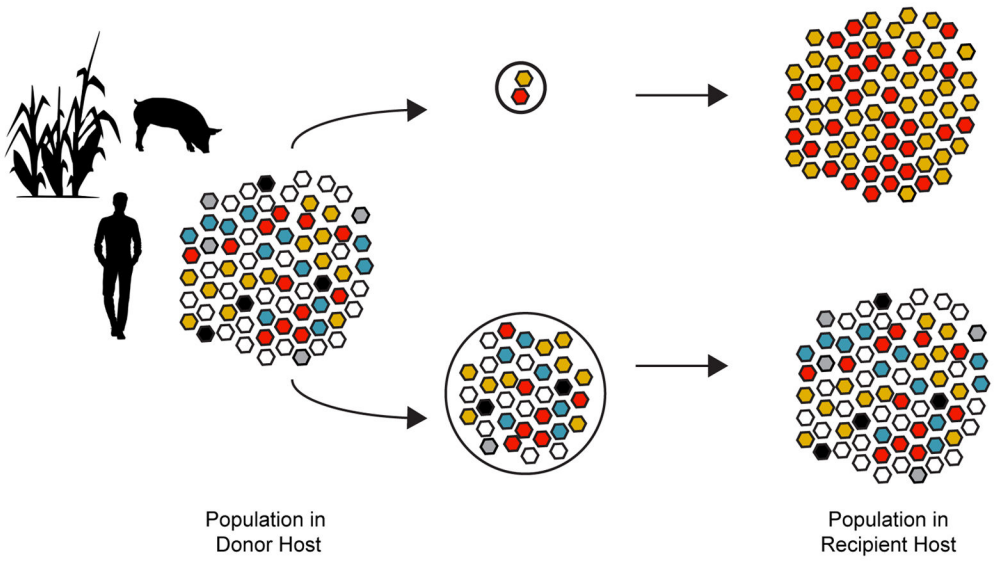

Figure 1.

The effect of transmission bottlenecks on viral diversity. In a variety of hosts (e.g. humans, pigs, plant shown here), stringent bottlenecks (top) limit the size and diversity of a population and drastically alter their composition. The large populations that pass through loose bottlenecks (bottom) allow for transmission of rare variants. As a result the diversity of the population in the recipient approximates that of the donor.

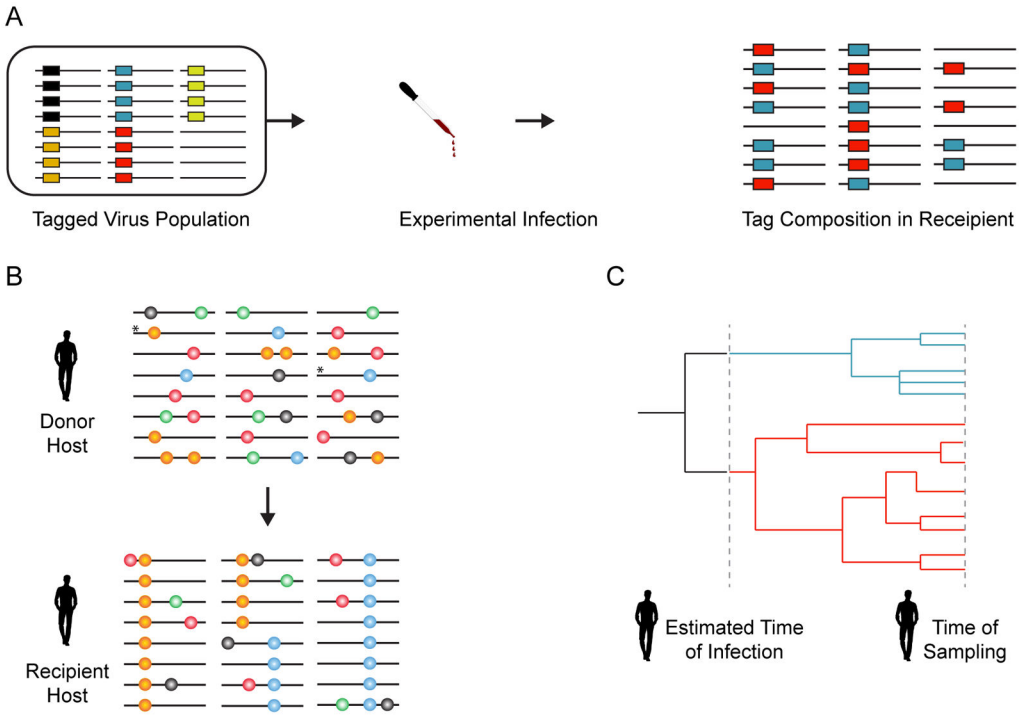

Figure 2.

Measuring transmission bottlenecks. (A) The number of donor-derived, neutral markers detected in the recipient is an indication of the stringency of the transmission bottleneck. Here, 3 of the 6 markers were transmitted suggesting a stringent bottleneck. (B) Shared diversity data from natural systems can be used to estimate a bottleneck. In the example, only two donor genotypes, denoted with *, were transmitted to the recipient suggesting a stringent bottleneck. Other *de novo* mutations arise on these backgrounds after transmission. (C) Coalescent models allow one to work backward from the time of sampling and estimate the number of genotypes that could plausibly give rise to the observed diversity. In this case, the two lineages are traced back to two genetically distinct variants present at transmission.