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Variability in viral pathogenesis: modeling the dynamic of acute and persistent infections

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Virus infection often results in diverse outcomes. This variability of virus pathogenesis is not well understood. Here we revise theoretical arguments to further our understanding of factors controlling infection and its severity. We propose that variability in these factors results in different clinical outcomes, which ultimately ensure virus reproduction.

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Virulence versus transmission: a trade-off

A link between parasite virulence and its transmission efficiency is a paramount concept in modern epidemiology. The trade-off between these two pathogen's features has been studied and discussed for decades.

The original view that prevailed in 1880s–1990s was that pathogenicity (here and below also termed 'virulence') and transmission rates evolve independently. The best virus, according to this classical view, causes very small pathogenesis but replicates really well and therefore transmits at a high rate to other hosts (Figure 1a). Over time, the virus and the host coevolve and adapt to each other and the 'most convenient' strategy is to coexist in the long term. Historically this view was backed up by a classical in-nature experiment made on rabbit myxoma virus. When introduced in 1950 into Australia to limit European rabbit population, highly-virulent myxoma virus killed >99% of infected hosts. However, as the epidemic progressed, virulence appeared to decrease gradually within 15–20 years [1•].

An entirely different view on virulence and adaptation emerged in 1980s. A mathematical model predicted the existence of a trade-off between mortality and transmission [2•,3]. The hypothesis, introduced by Anderson and May [4••] and Ewald [5•], assumed that host resources that could be used by the virus are limited. Therefore, increasing viral replication – and thus transmission – without harming the host is not possible. Transmission increases as a function of pathogenesis.

The trade-off hypothesis is formulated in terms of pathogen's fitness. Fitness is defined as the 'reproduction number' (R_0), the average number of hosts newly infected with virus from a previously infected host [6]:

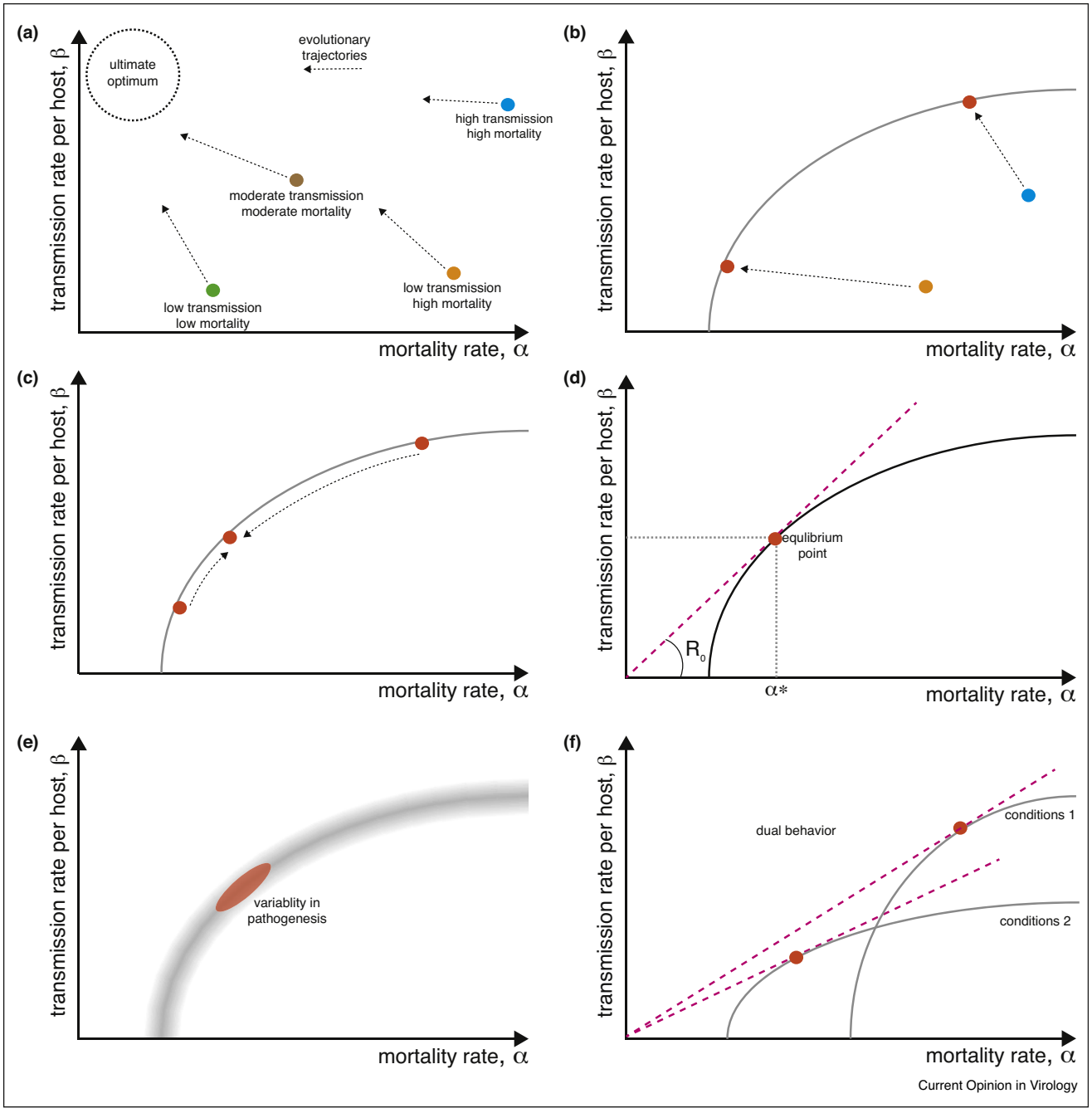
$$R_0 = \beta S/(\mu + \alpha + \gamma)$$

Here S is the density of susceptible hosts in the population, β is the transmission rate of virus per susceptible host per unit time, μ, α and γ are host's rates of natural death, the death rate due to infection, and the recovery rate from infection. The combined parameter βS represent the average number of new individuals infected by a single infected host per unit time and $(\mu + \alpha + \gamma)^{-1}$—the average time of host's exposure to infection.

According to the trade-off hypothesis, higher transmission comes at a cost to the host fitness. In other words, there is a minimal harm that pathogen must inflict on the host. The basic Susceptible-Recovered-Infected models [2] measure the minimal pathogenicity as a reduction in either the host lifespan or host reproduction due to the viral infection, or both. The transmission rate plotted against the minimal pathogenicity is called 'the tradeoff curve' (Figure 1b, dashed curve). This curve limits the area on the chart potentially accessible to a pathogen. The existence of that limited area expresses the main idea by Anderson and May [4••] and Ewald [5•] that one cannot have very high replication and transmission without causing high pathogenicity.

In the long-term, as we discuss below in more detail, the system host-pathogen arrives at an equilibrium represented by a point on the tradeoff curve (Figure 1b). In this situation, the variant composition in the virus population [7,8] are in transient equilibrium with the host. As time passes by, the transient equilibrium point slides along the tradeoff curve until it arrives at the ultimate long-term equilibrium (Figure 1c). The coordinates of the ultimate equilibrium can be found graphically as a tangent of the curve that passes through the origin of the

Figure 1



(a) Hypothesis of avirulence of well-evolved viruses. All viruses are evolving to lower their virulence (here virus-related mortality rate per time unit, α) and increase transmission (rate per susceptible host per time unit, β). This assumes independent evolution of these two parameters. Dots show different virus strains or species. **(b)** Hypothesis of tradeoff (interdependence) of virulence and transmission due to host-scale factors. Paths show direction of dynamics of host population toward local equilibrium. Curve with dots: different possible local equilibria (depending on initial values α and β). Thus, virulence and transmissibility, although defined on the epidemiological scale, are mutually restricted due to underlying host-scale factors. **(c)** A single tradeoff point. The arrows along the curve show direction of long-term genetic evolution toward stable end-point equilibrium. **(d)** Long-term equilibrium. μ and γ are natural mortality and recovery rates correspondingly. The straight line is the tangent of the curve. Fitness (R_0) could be found as a tangent of this curve. **(e–d)** Hypothesis: variability in ecological factors leads to a fluctuating of tradeoff curve resulting in viruses with variable pathogenesis (d). Existence of two sparse conditions results in two tradeoff curves and viruses with dual pathogenesis (e).