evolution of virulence

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# Definitions

* **virulence**
  + (broad): decrease in a host’s fitness caused by a parasite.
  + (narrow): *per capita* rate of parasite-induced host mortality
* **resistance**: host’s ability to resist or minimize infection
* **tolerance**: host’s ability to support parasite infection without losing fitness
* **case mortality** (CM): fraction of hosts killed by infection
* Parasite-host interaction complicates the definition of virulence (assumes that a more virulent parasite is more virulent for *all* host genotypes/species)
* conceptually:
  + parasite load depends on balance between parasite *within-host reproduction rate* and host’s *parasite clearance rate*
  + virulence depends on parasite load and per-copy parasite *pathogenicity* and host *tolerance*
  + this establishes the terms of the arms race, but these components can’t be separated if we look at a single host-parasite pair (parasite virulence is often confounded with host tolerance)
* all in an arms race rather than RQ context

# Classical dogma

* Parasites evolve lower virulence over time “for the good of the species”. Group-selectionist *but* some evidence?
  + syphilis; first seen in Europe in 1495 (the “Great Pox”) (Knell 2004)
    - origins? (previously misdiagnosed; evolved increased virulence; from Africa; from the New World)
    - virulence decreased rapidly over 50 years (maybe even 5-7 years?)
  + *virgin-soil epidemics*: smallpox, etc. (Crosby 1976; Ostler 2020) (probably *not* virulence: lack of genetic resistance, previous exposure, societal breakdown, effects of colonization?)
* sampling bias?
  + biocontrol examples always select for maximal virulence
  + mild introductions may not be noticed

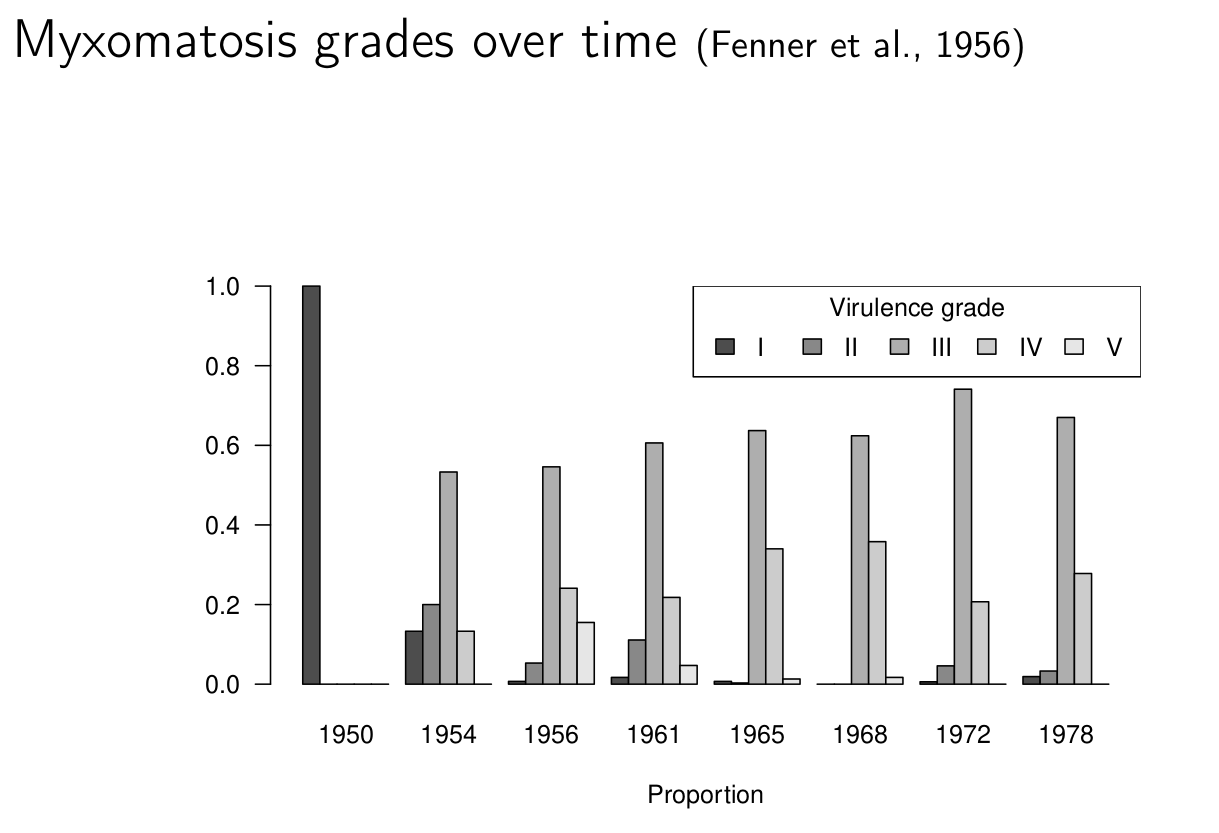
# Tradeoff theory

* Intermediate virulence evolves due to host-level selection (group theory returns); a tradeoff between transmission *rate* (infections/host/time) and virulence (*defined as mortality/time*) leads to maximum (total transmission per generation) at **intermediate** virulence.
* conceptually, mediated by parasite replication rate or load

## Example: myxomatosis

Viral disease; mild in Brazilian rabbits (*Sylvilagus brasiliensis*), virulent in European rabbits (*Oryctolagus cuniculus*). Mosquito- and flea-borne. Introduced (several times) in Australia to control introduced rabbits, finally spread 1950-1951. Case mortality originally >99%, populations initially decreased by 90%. CM initially dropped to 90%, then further. Resistance: test by infecting laboratory rabbits that haven’t evolved. CM of grade III strain drops from 90% to about 50% as populations experience more epizootics. At the same time mean virus grade drops from I to III, then rebounds.

Evidence for tradeoff theory: Higher grades (higher case mortality) also have faster mortality (<13 days to >50 day survival as CM goes from >99% to <50%). Skin virus *titer* is also higher (and increases faster with time) for higher grades. Mosquito infection probability is proportional to skin titer. (Some biological complications.)



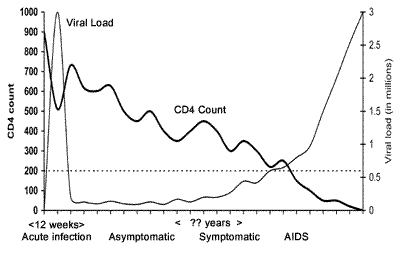
Bottom line: myxomavirus probably still reduces populations somewhat, but the Australians continue to look for other biocontrol solutions (calicivirus, rabbit haemhorrhagic disease).

Genomic analysis: Kerr et al. (2012), Kerr et al. (2013), Kerr et al. (2022)

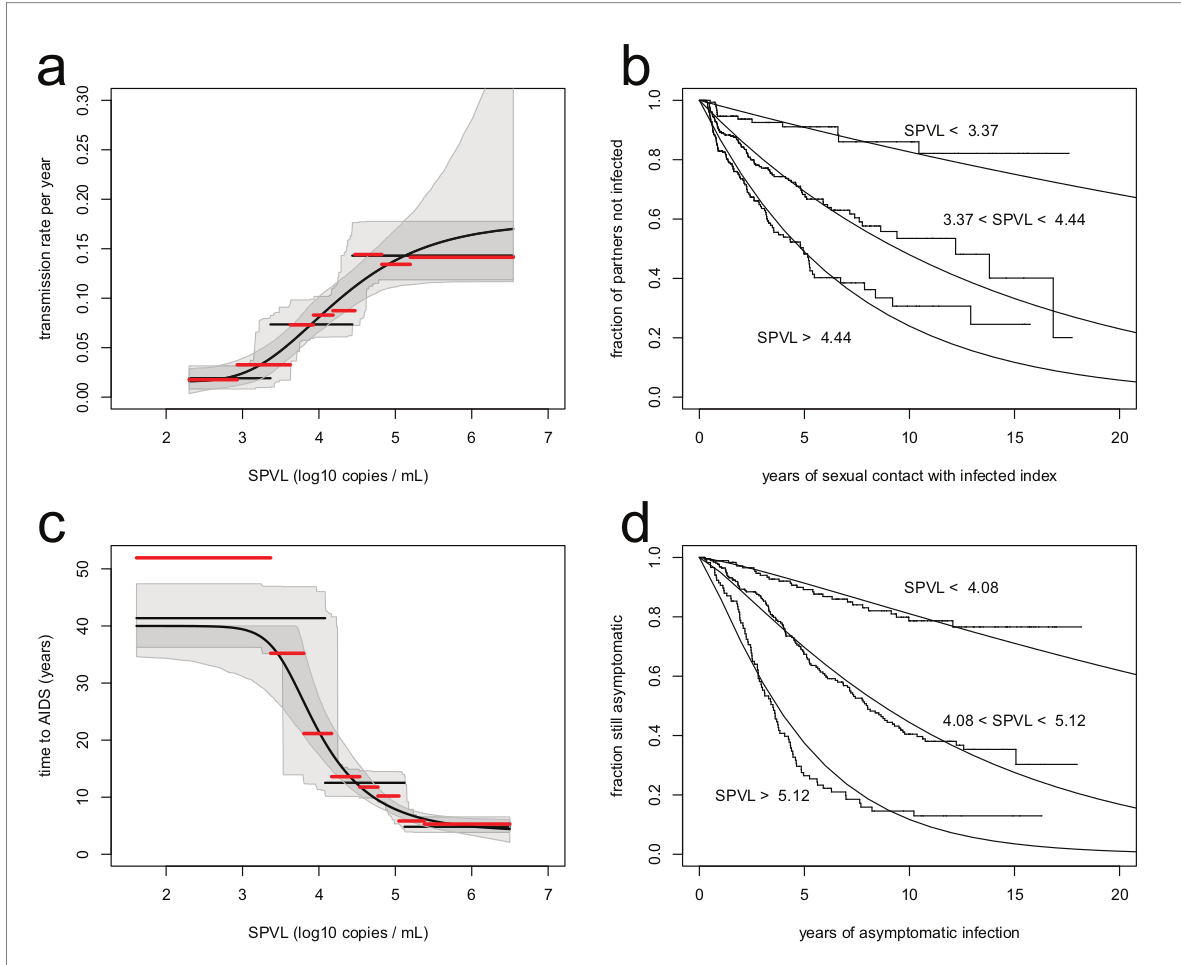
* Australia
  + some mutations with clear virulence effects (insertion disrupts reading frame involving cell cycle; deletion affects immunosuppressive pathway)
  + **probably** “attenuation-restoration” in Australia: attenuating mutations fixed, then restored
* Britain
  + premature stop codon disrupts immunosuppression
  + parallel evolutions, but different substitutions

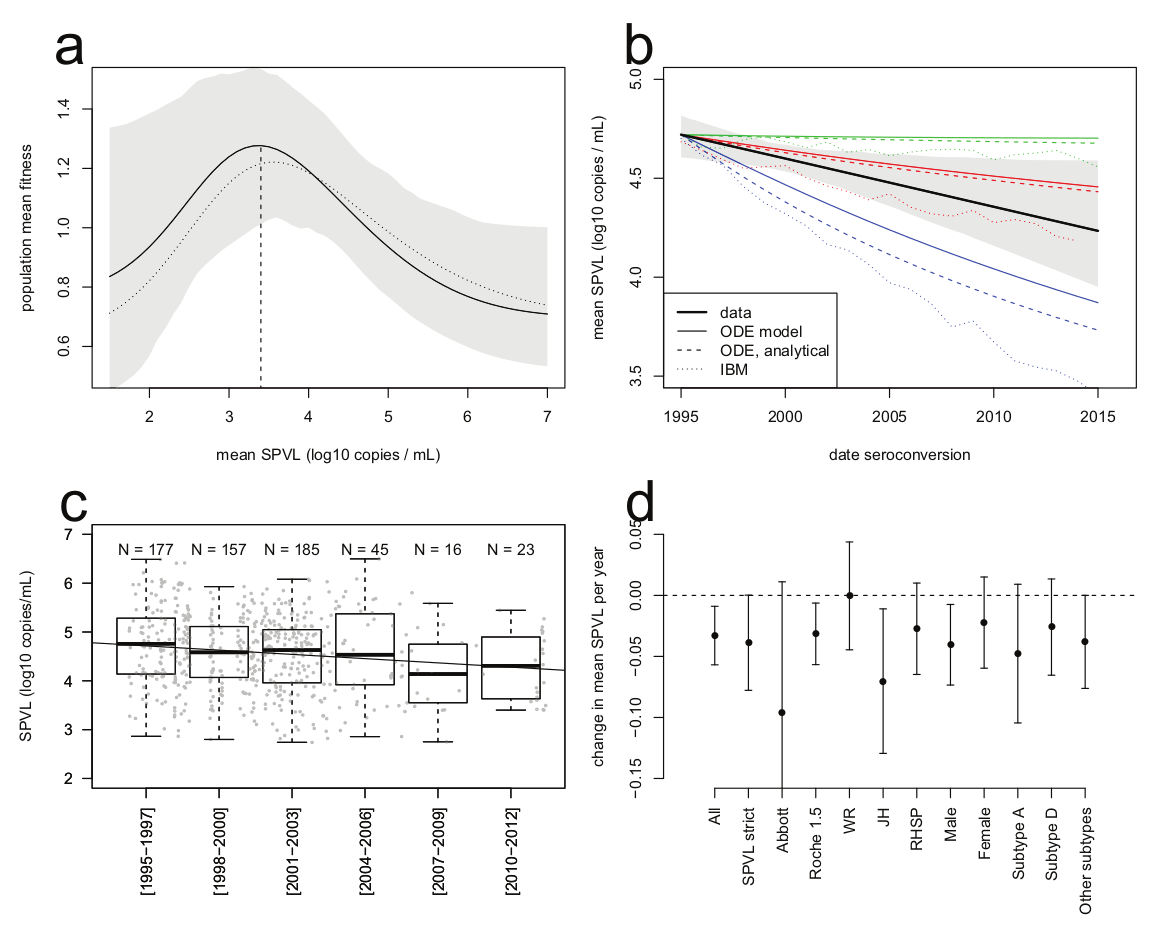
## Example: HIV

* Correlations among
  + *setpoint viral load*
  + *time to progression* or *rate of CD4 decline* (mechanisms still poorly understood! within-host evolution for diversity, virulence, immune escape? immune aging?? accumulation of opportunistic infections?)
  + *transmission probability* (as measured in *serodiscordant couples*; *Rakai cohort*)
* no longer ethically measurable

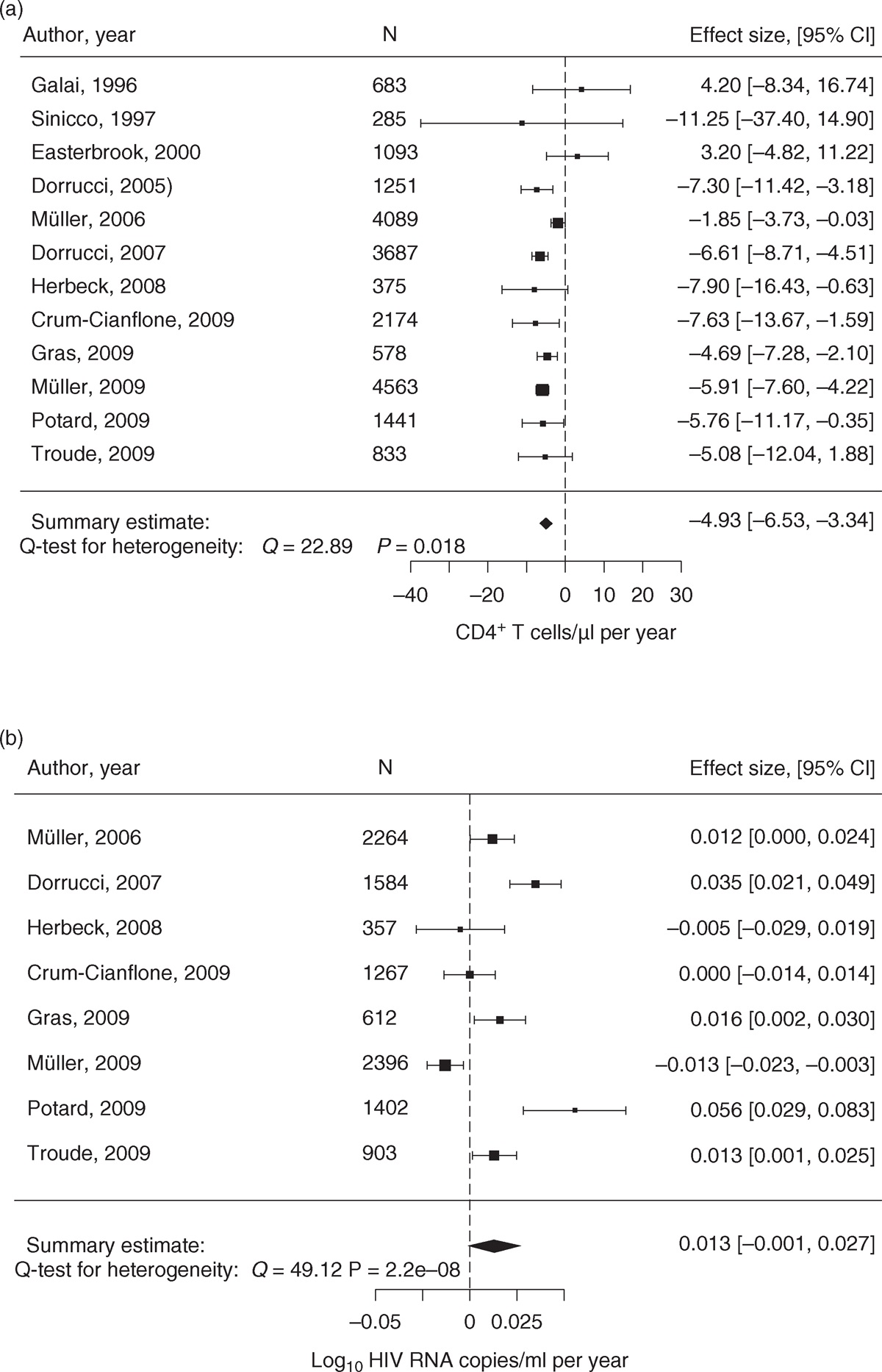


<https://www.thebodypro.com/article/course-hiv-disease>



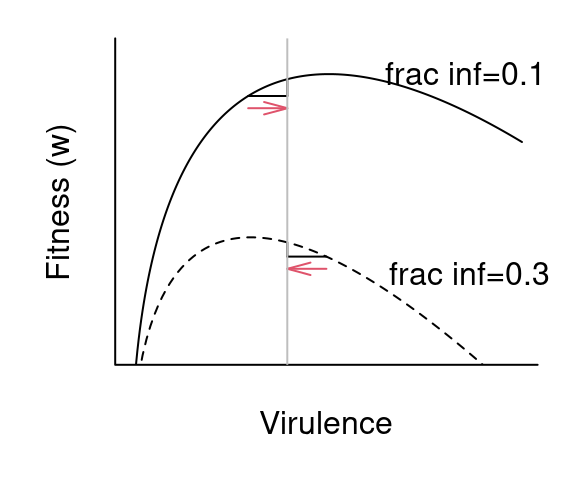


* some suggestion of overall increase in virulence (decreased CD4 count/increased viral load)
* highly variable (e.g. increasing in Italy (Müller et al. 2009)? attenuating due to spread of less virulent subtype C (Ariën, Vanham, and Arts 2007)? decreasing in Uganda (Blanquart et al. 2016)? increasing overall (Herbeck et al. 2012)?



## Theory

* if there is a tradeoff, we would expect expect strong effects of **transmission mode**
  + vector-borne > direct
  + high virulence for “necrotransmission” (via dead hosts: anthrax, chronic wasting disease)
  + horizontal transmission > vertical
  + needle-borne > STD?
  + environmental (water-borne, e.g. cholera) > direct
* does higher overall transmission rate (due to population density, poor hygiene, etc.) select for higher transmission?
* **facultative** parasites (e.g. soil-borne microbes with a **facultative** stage) should be more virulent
* “curse of the pharaoh”: effect of resting stages? (Bonhoeffer, Lenski, and Ebert 1996)
* spatial restriction should? decrease virulence (Kamo and Boots 2006)
* Maximizing :



* “Virulence” could be effect of host mortality, or rapid clearance.

## Within-host competition

* basic tradeoff theory assumes one infection/strain per host
* effects of mutation, **superinfection**: within-host competition
* tends to *increase* optimal virulence

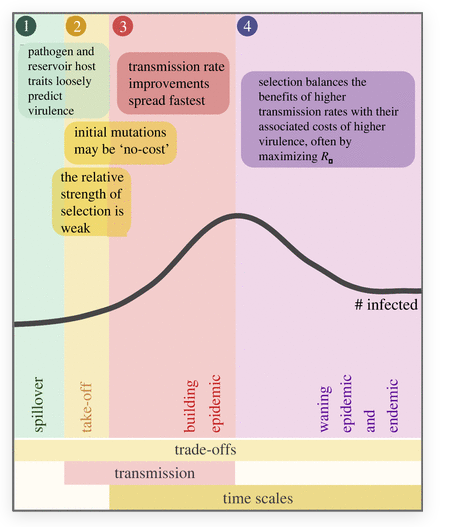
## Short-sighted evolution

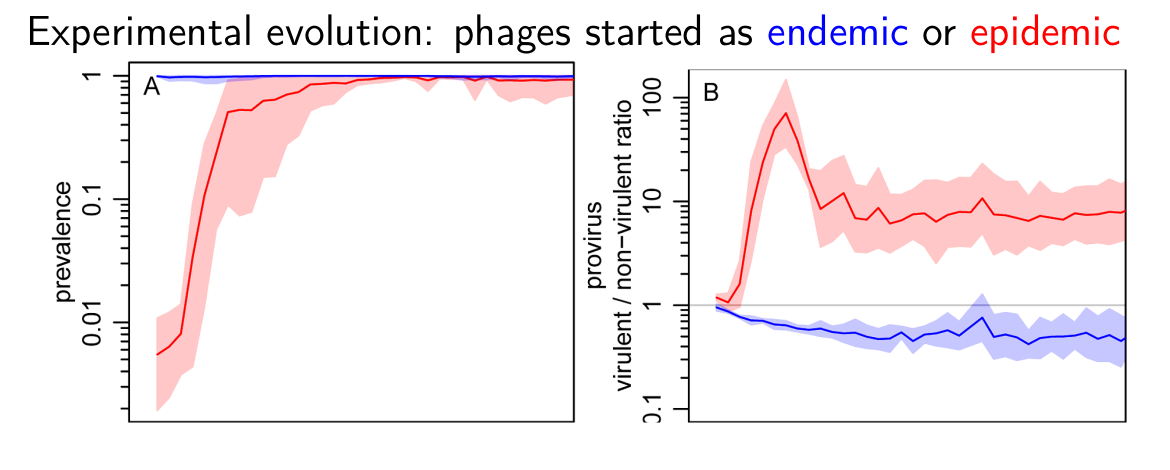
* sometimes evolution is just stupid (Levin and Bull 1994)
* meningitis-producing, paralytic polio strains (central nervous system tropism)
* HIV [most transmission probably occurs during acute phases]

## Epidemic vs. endemic phases; transient virulence

* Most theory assumes that disease is at an *endemic equilibrium*, so that *lifetime fitness* (i.e.  maximization) is what matters
  + this also means that increasing overall transmission (due to population density, poor hygiene, etc.) **doesn’t** select for higher virulence
* During the exponential growth phase of an epidemic, *speed of increase* ( maximization) is what matters
  + optimal virulence is higher than for endemic equilibrium
* We expect *transient* selection for higher virulence at the beginning of an epidemic

(Frank 1996; Bolker, Nanda, and Shah 2010; Visher et al. 2021; Day and Proulx 2004; Berngruber et al. 2013; Park and Bolker 2017)





## Effects of vaccines and treatment

* evolution due to **risk compensation** (Massad et al. 2006)?
* evolution of higher virulence in unvaccinated people due to “leaky” vaccination (Gandon et al. 2001)?
* mouse malaria: (Mackinnon and Read 2004; Mackinnon, Gandon, and Read 2008); consistent with “arms race” upregulation of replication
* increased virulence in Marek’s disease: reduced host generation time or effects of leaky vaccine? (Atkins et al. 2013)
* [in HIV due to antiretrovial therapy](herbeck_evolution_2016)?

Mackinnon, Gandon, and Read (2008):

a cautionary approach to the widespread use of anti-replication or anti-disease vaccines seems justified. Ideally, this means combining such vaccines with transmission-blocking vaccines, bednets, drugs, housing improvements and other transmission-reducing measures

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