

## *evolution of virulence*

27 February 2022

### *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”) (Kneill 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\_disease\_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  $R_0$  (total transmission per generation) at **intermediate** virulence.
- conceptually, mediated by parasite replication rate or load

### *Example: myxomatosis*

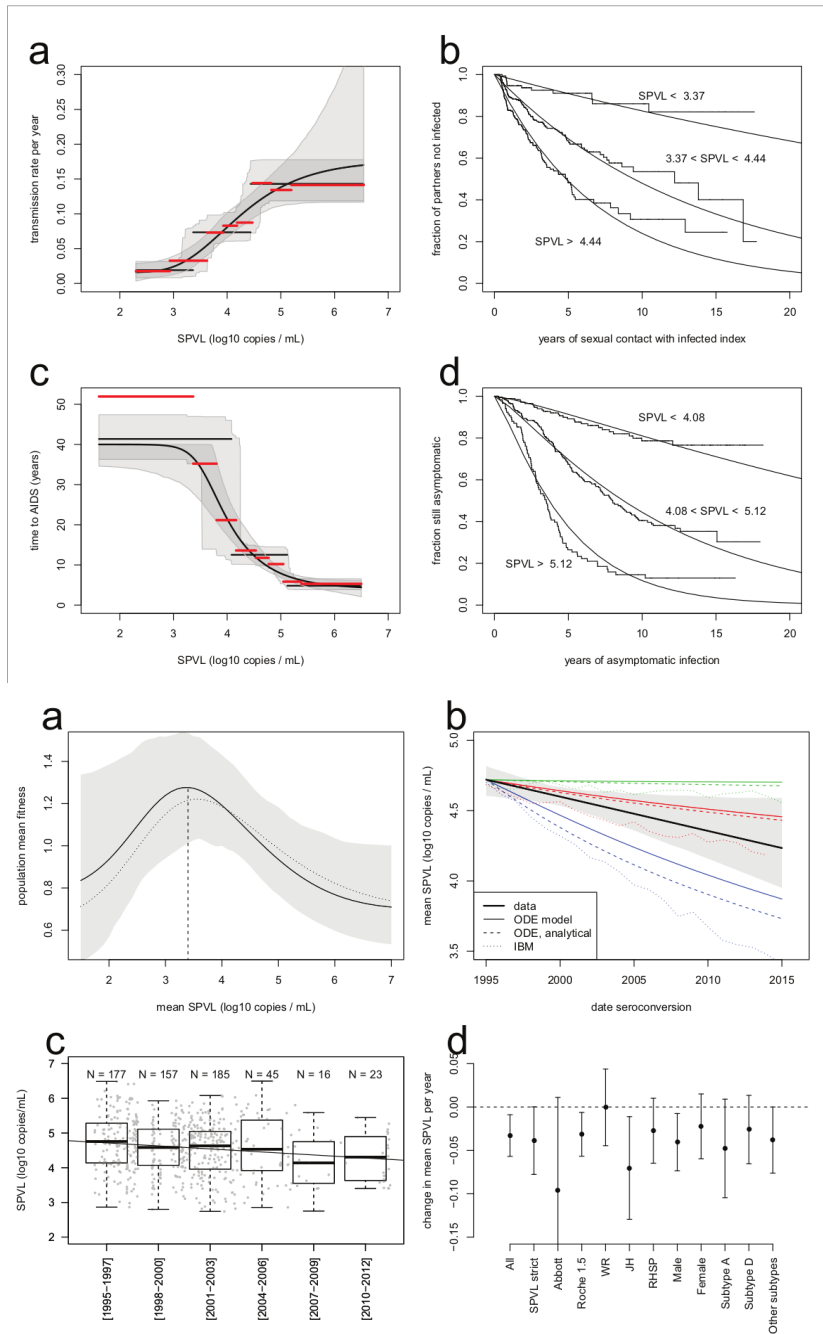
Viral disease; mild in Brazilian rabbits (*Sylvilagus brasiliensis*), virulent in European rabbits (*Oryctolagus cuniculus*). Mosquito- and flea-borne. Introduced (several times) in Australia to control introduced rabbits, finally spread 1950-1951. Case mortality originally >99%, populations initially 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 haemorrhagic disease).

### *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*)
- probably no longer ethically measurable

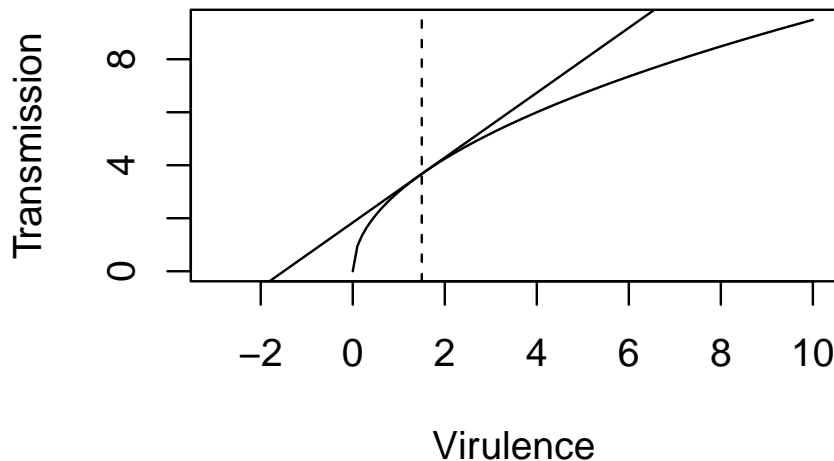


- highly variable [

### Theory

- if there is a tradeoff, we would 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  $R_0$ :



- “Virulence” could be effect of host mortality, or rapid clearance.
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#### *Within-host competition*

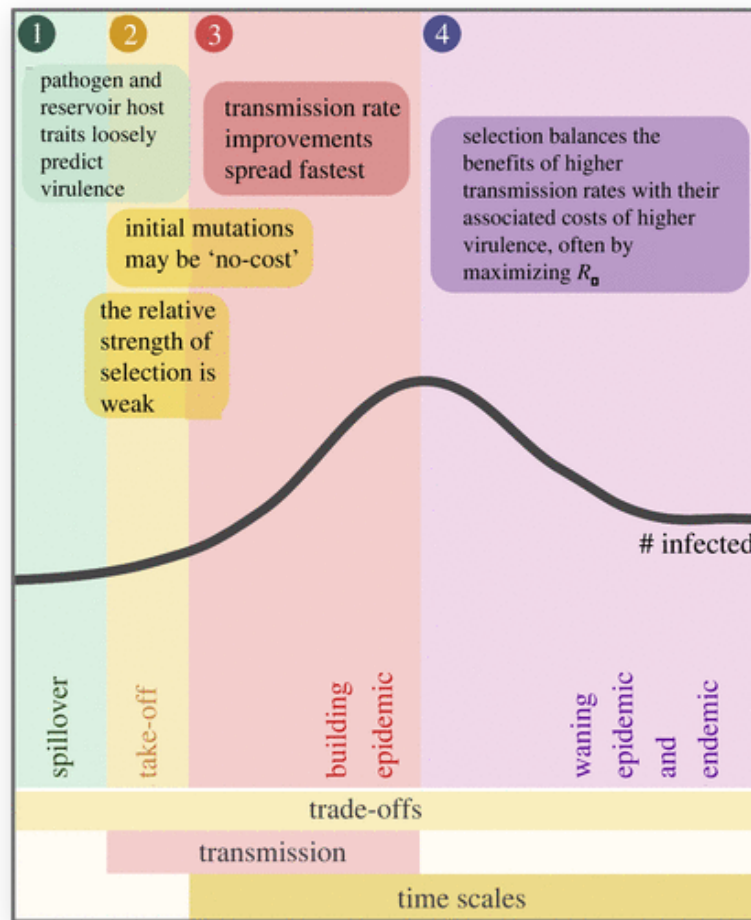
- basic tradeoff theory assumes one infection/strain per host
- effects of mutation, **superinfection**: within-host competition

#### *Short-sighted evolution*

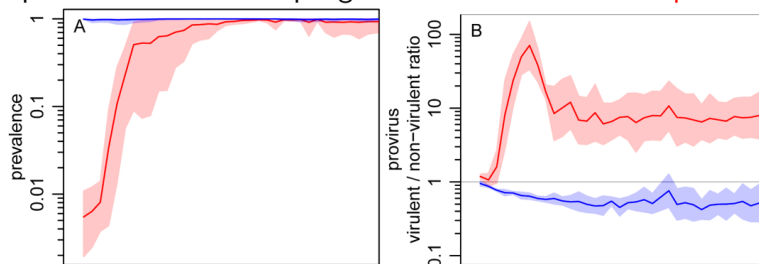
- sometimes evolution is just stupid (Levin and Bull 1994)
- meningitis-producing, paralytic polio strains (central nervous system tropism)
- HIV [most transmission probably occurs during acute phases]

### *Epidemic vs. endemic phases; transient virulence*

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



Experimental evolution: phages started as **endemic** or **epidemic**



### *Effects of imperfect vaccines*

- 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)

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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