evolution of virulence

23 October 2023

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 R_0 (total transmission per generation) at **intermediate** virulence.

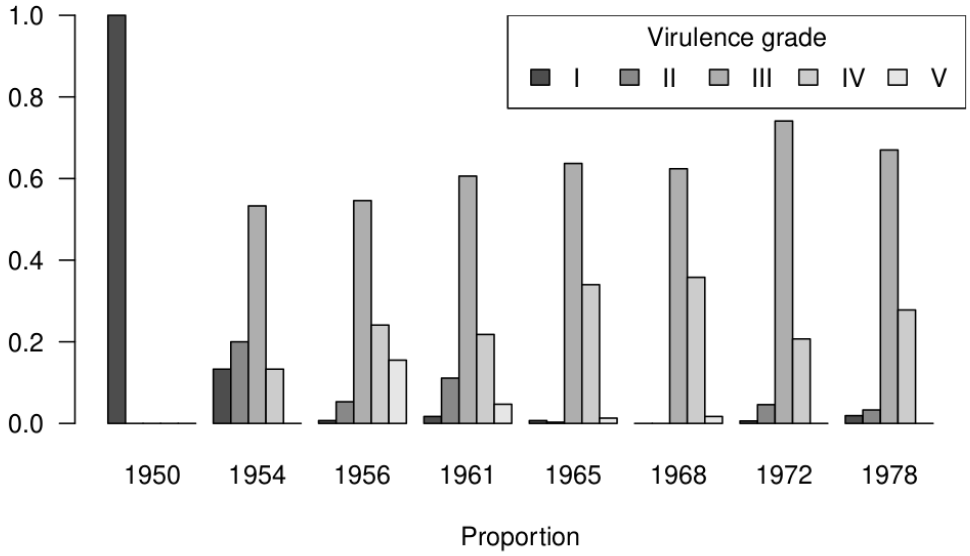
- conceptually, mediated by parasite replication rate or load (cf spore production/*Daphnia* fecundity example (Decaestecker et al. 2007)

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.)

Myxomatosis grades over time (Fenner et al., 1956)



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

Lab experiments on titers, transmission probabilities, etc. etc. etc. (Fenner, Day, and Woodroofe 1956); simulation model (Dwyer, Levin, and Buttel 1990)

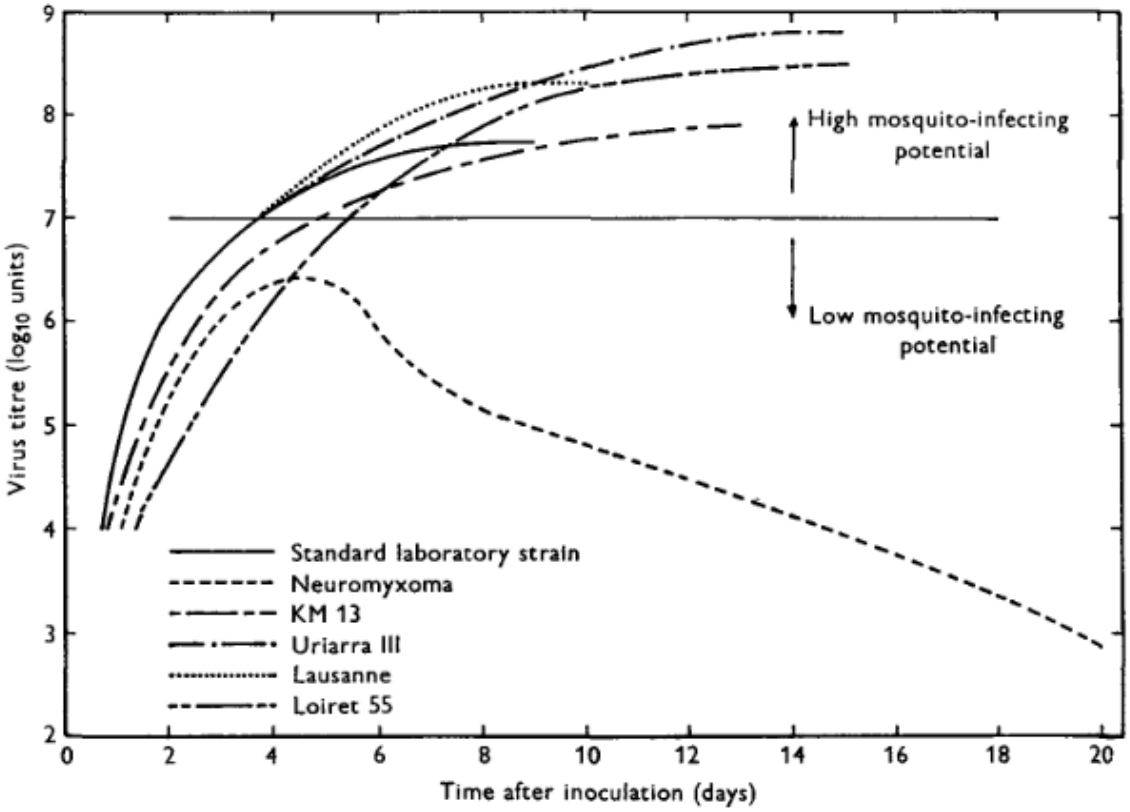


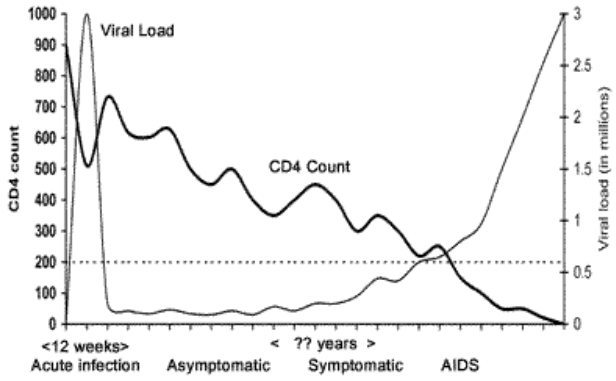
Fig. 1. The titre of virus in slices of skin taken from the surface of lesions produced by the intradermal inoculation of rabbits with large doses ($10^{4.3}$ rabbit-infectious doses) of various strains of myxoma virus.

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

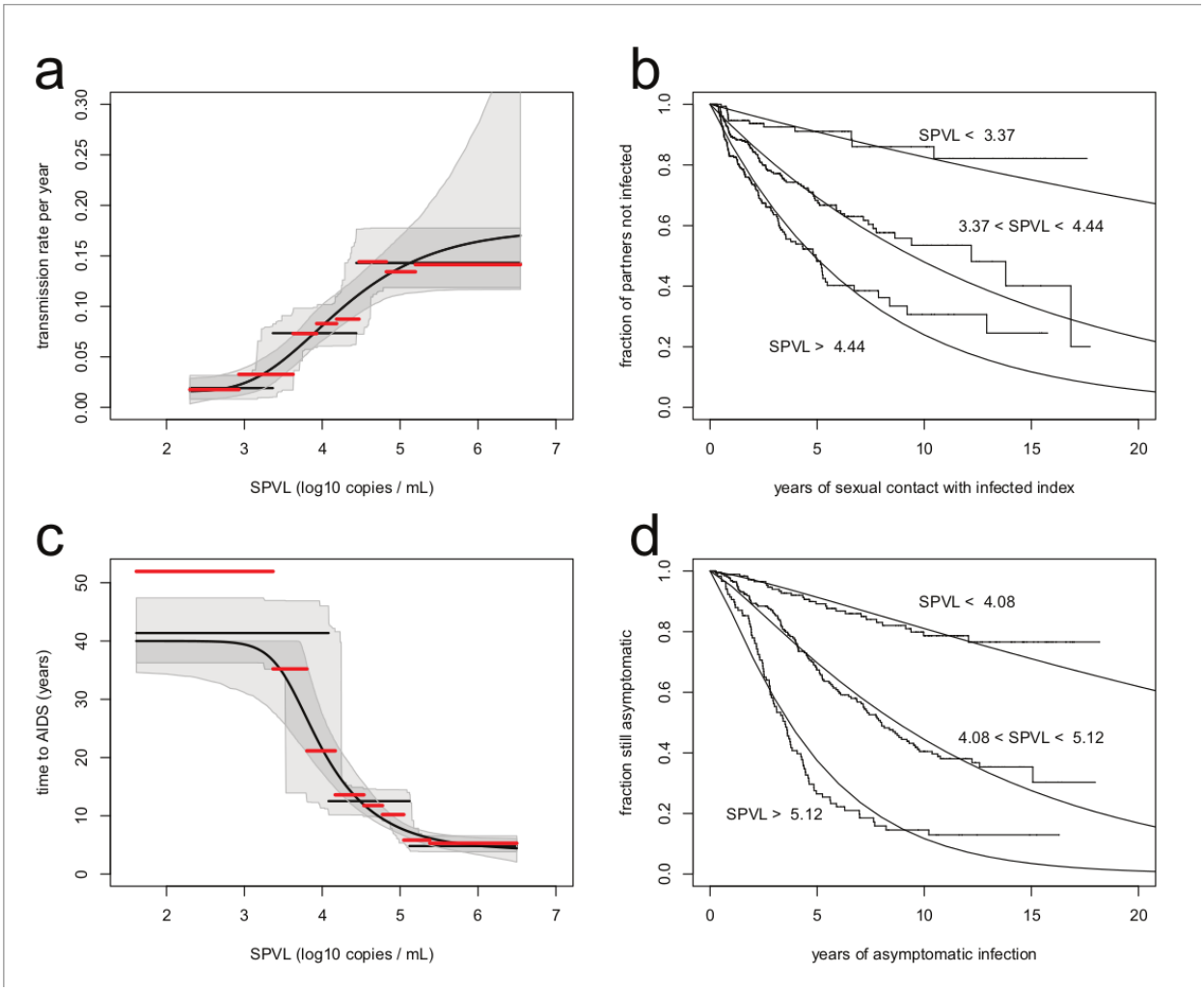
- Australia
  - some mutations with clear virulence effects (insertion disrupts reading frame involving cell cycle; deletion affects immunosuppressive pathway)
  - **probably** "attenuation-restoration" in Australia: attenuating mutations fixed, then restored
- Britain
  - premature stop codon disrupts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

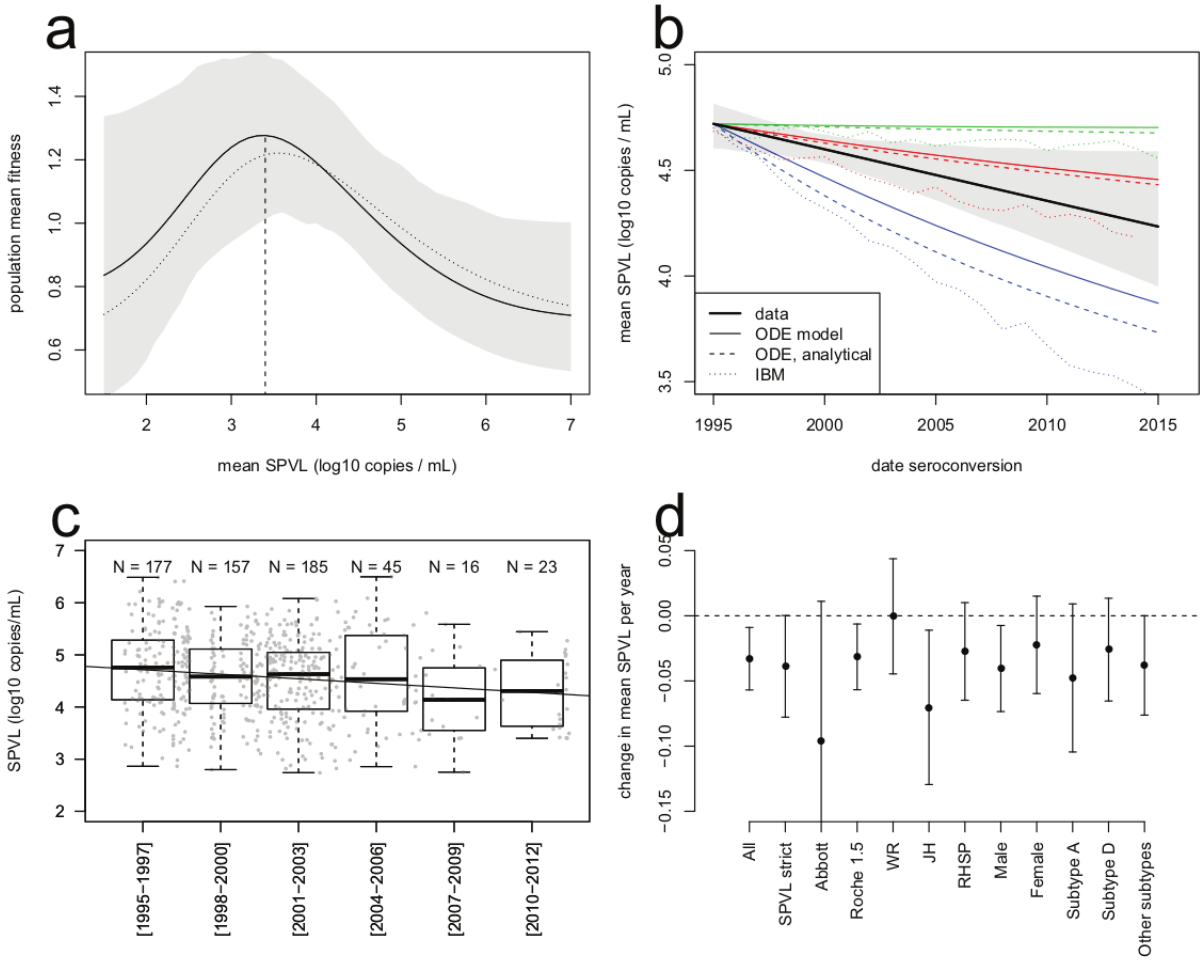
Example: HIV

- 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



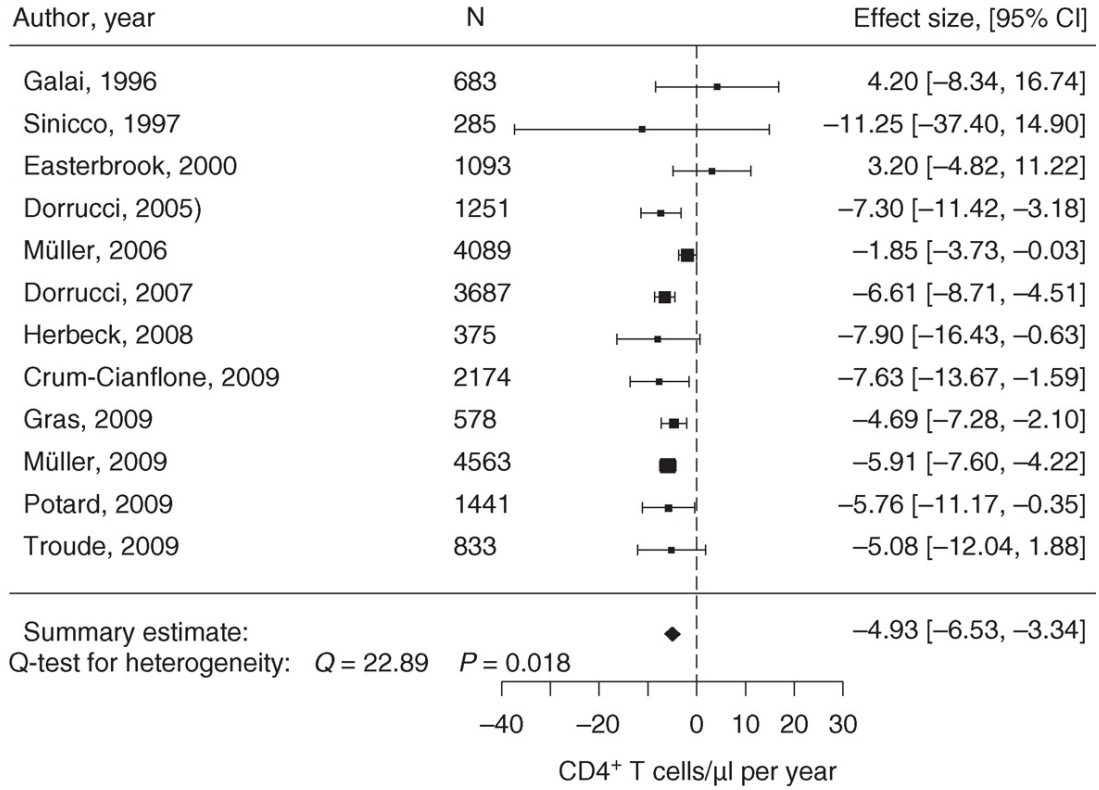
https://www.thebodypro.com/article/course-hiv-disease



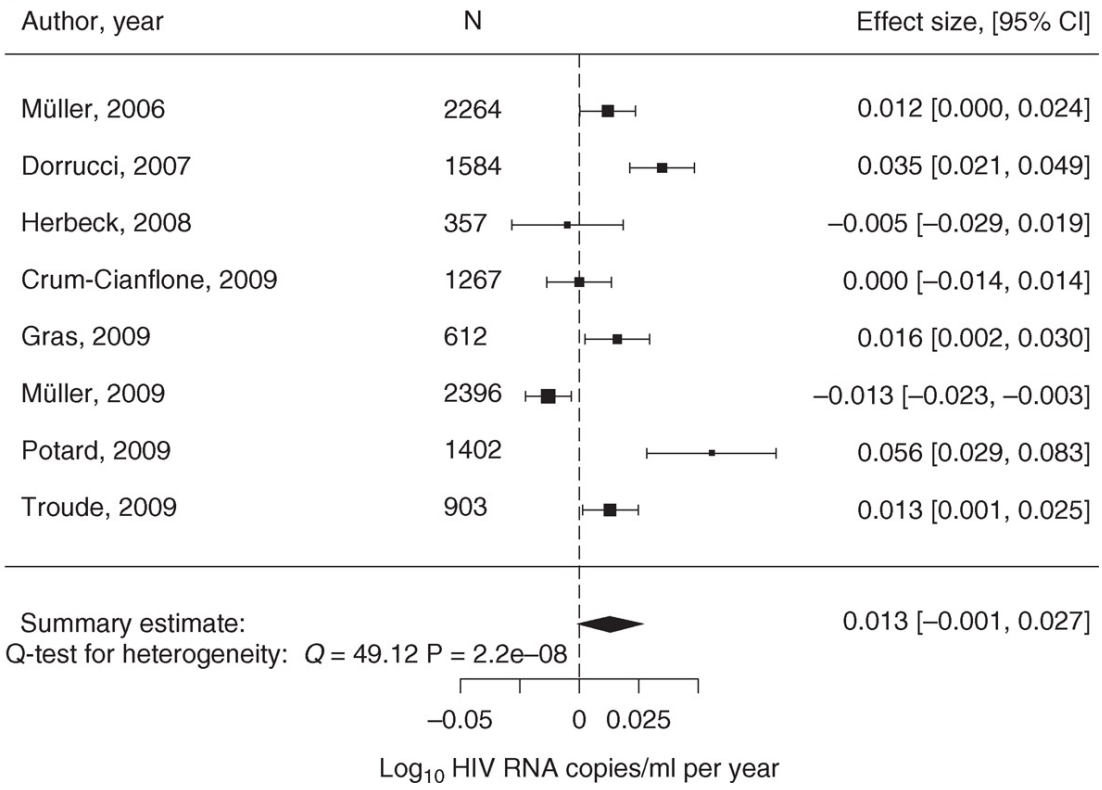


- some suggestion of overall increase in virulence (decreased CD4 count/increased viral load)
- highly variable (e.g. increasing in Italy (Müller et al. 2009)? attenuating due to spread of less virulent subtype C (Ariën, Vanham, and Arts 2007)? decreasing in Uganda (Blanquart et al. 2016)? increasing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

(a)

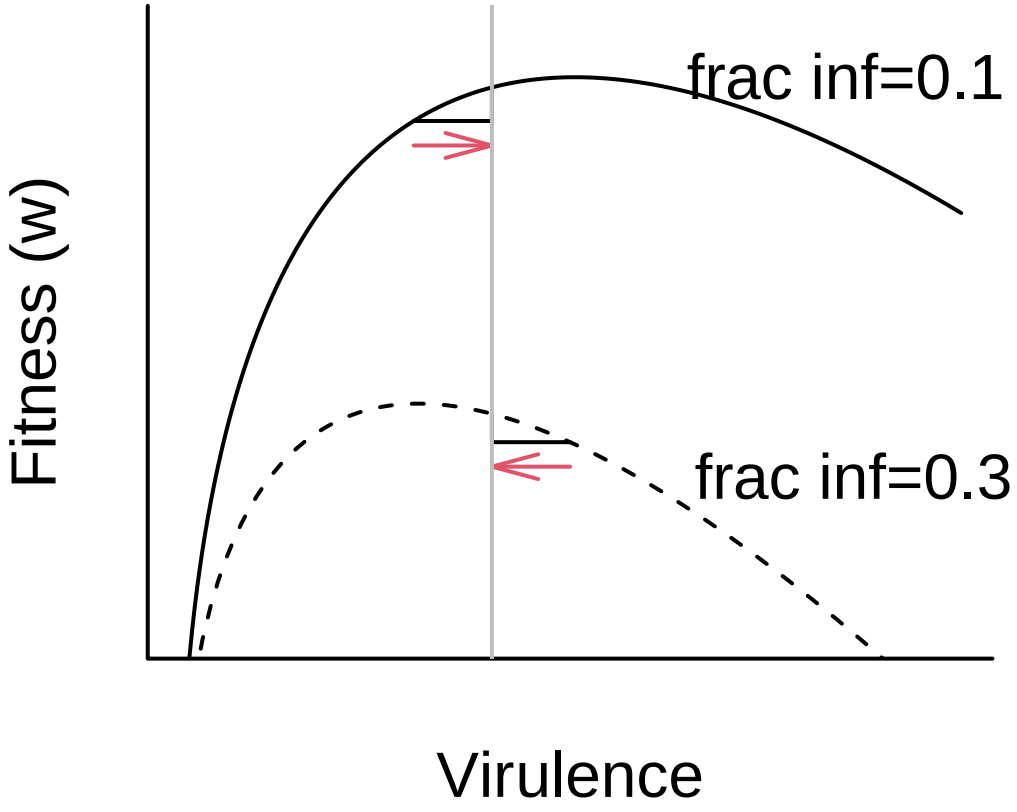

Author, year
N
Effect size, [95% CI]
Galai, 1996 683 4.20 [–8.34, 16.74]
Sinicco, 1997 285 –11.25 [–37.40, 14.90]
Easterbrook, 2000 1093 3.20 [–4.82, 11.22]
Dorrucci, 2005) 1251 –7.30 [–11.42, –3.18]
Müller, 2006 4089 –1.85 [–3.73, –0.03]
Dorrucci, 2007 3687 –6.61 [–8.71, –4.51]
Herbeck, 2008 375 –7.90 [–16.43, –0.63]
Crum-Cianflone, 2009 2174 –7.63 [–13.67, –1.59]
Gras, 2009 578 –4.69 [–7.28, –2.10]
Müller, 2009 4563 –5.91 [–7.60, –4.22]
Potard, 2009 1441 –5.76 [–11.17, –0.35]
Troude, 2009 833 –5.08 [–12.04, 1.88]
Summary estimate: –4.93 [–6.53, –3.34]
Q-test for heterogeneity: Q = 22.89 P = 0.018
–40 –20 0 10 20 30
CD4+ T cells/µl per year

(b)


Author, year
N
Effect size, [95% CI]
Müller, 2006 2264 0.012 [0.000, 0.024]
Dorrucci, 2007 1584 0.035 [0.021, 0.049]
Herbeck, 2008 357 –0.005 [–0.029, 0.019]
Crum-Cianflone, 2009 1267 0.000 [–0.014, 0.014]
Gras, 2009 612 0.016 [0.002, 0.030]
Müller, 2009 2396 –0.013 [–0.023, –0.003]
Potard, 2009 1402 0.056 [0.029, 0.083]
Troude, 2009 903 0.013 [0.001, 0.025]
Summary estimate: 0.013 [–0.001, 0.027]
Q-test for heterogeneity: Q = 49.12 P = 2.2e–08
–0.05 0 0.025
Log10 HIV RNA copies/ml per year

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 R_0:



- "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

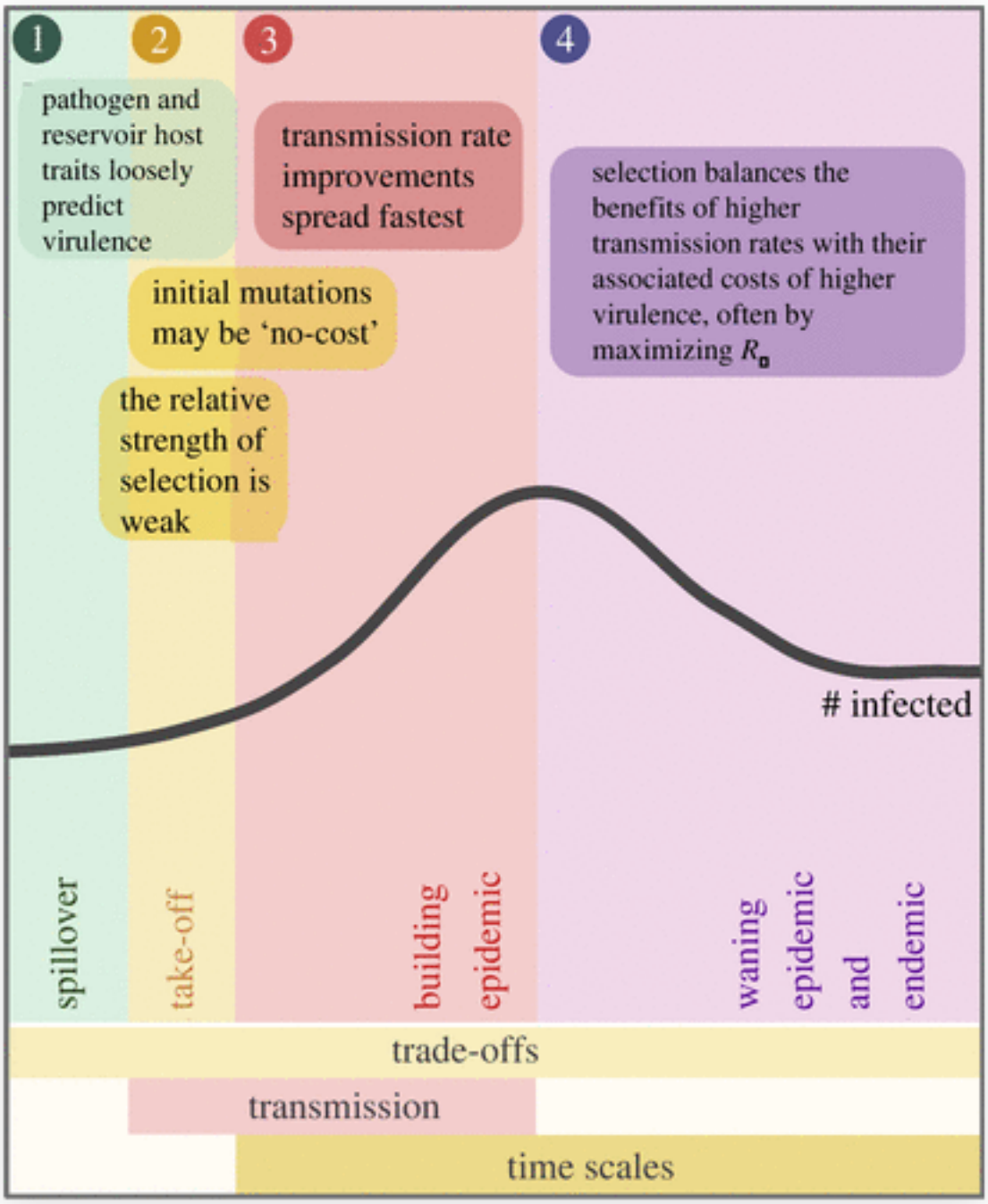
- sometimes evolution is just stupid (Levin and Bull 1994)

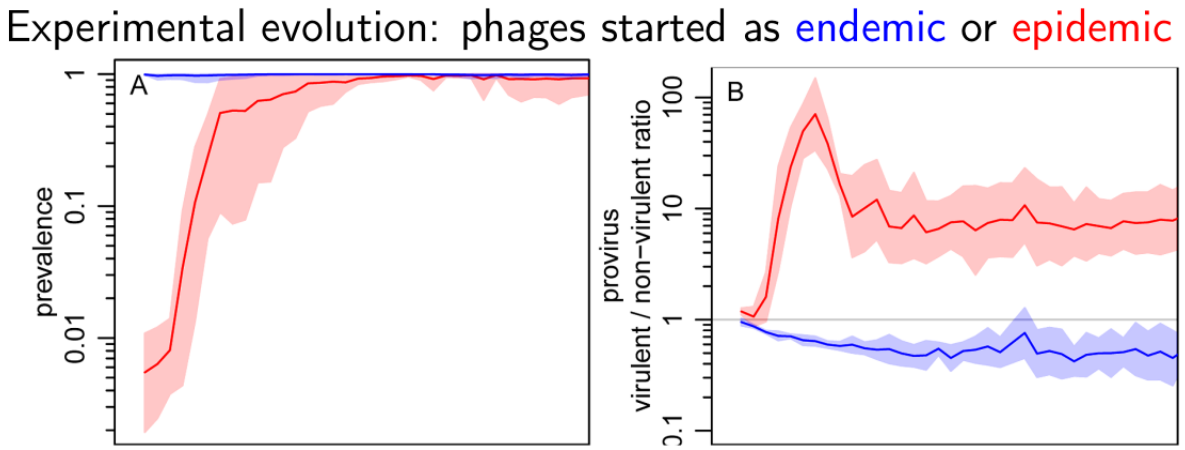
- meningitis-producing, paralytic polio strains (central nervous system tropism)
- HIV [most transmission probably occurs during acute phases]

Epidemic vs. endemic phases; transient virulence

- Most theory assumes that disease is at an *endemic equilibrium*, so that *lifetime fitness* (i.e. R_0 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* (r 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)


1
2
3
4
pathogen and reservoir host traits loosely predict virulence
initial mutations may be 'no-cost'
the relative strength of selection is weak
transmission rate improvements spread fastest
selection balances the benefits of higher transmission rates with their associated costs of higher virulence, often by maximizing R_0
infected
spillover
take-off
building epidemic
waning epidemic and endemic
trade-offs
transmission
time scales



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: (Margaret J. Mackinnon and Read 2004; M. J. 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 antiretroviral therapy?

M. J. 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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