Lecture 16

Evolution of virulence II

Today:

The trade-off hypothesis and Paul Ewald's view: route and timing of transmission determines virulence

- Transmission and virulence de-coupled: coincidental evolution

- Transmission and virulence de-coupled: Short-sighted evolution
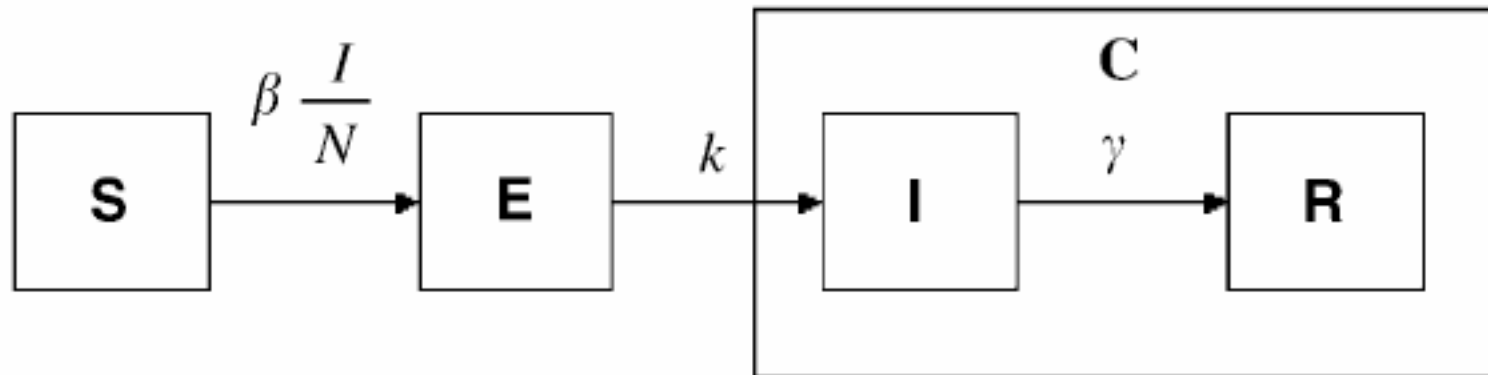
- Answer review questions

Fig. 1. A schematic representation of the flow of individuals between epidemiological classes. $\beta I/N$ is the transmission rate to susceptibles S from I; E is the class of infected (not yet infectious) individuals; k is the rate at which E-individuals move to the symptomatic and infectious class I; Infectious individuals (I) either die or recover at rate γ. C is not an epidemiological state but keeps track of the cumulative number of cases after the time of onset of symptoms.

The basic reproductive number R_0 measures the average number of secondary cases generated by a primary case in a pool of mostly susceptible individuals (Anderson and May, 1991; Brauer and Castillo-Chavez, 2000) and is an estimate of the epidemic growth at the start of an outbreak if everyone is susceptible. That is, a primary case generates $R_0 = \beta_0/\gamma$ new cases on the average where β_0 is the pre-interventions transmission rate and $1/\gamma$ is the mean infectious period. The effective

R_0: The basic reproductive rate

$$R_0 = \frac{\text{ß}N}{\alpha + b + v}$$

ß = rate constant of infectious transfer (transmissibility)

N = density of the susceptible host population

α = rate of parasite-induced mortality (virulence)

b = rate of parasite-independent mortality

v = rate of recovery

Table 1
Parameter definitions and baseline estimates obtained from the best fit of the model equations (1) to the epidemic-curve data of the Congo 1995 and Uganda 2000 outbreaks (Fig. 5)

Parameter	Definition	Congo 1995		Uganda 2000	
		Estim.	SD	Estim.	SD
β_0	Pre-interventions transmission rate (days^{-1})	0.33	0.06	0.38	0.24
β_1	Post-interventions transmission rate (days^{-1})	0.09	0.01	0.19	0.13
t_h	Time to achieve $\frac{\beta_0 + \beta_1}{2}$ (days)	0.71	(0.02, 1.39)[a]	0.11	(0,0.87)[a]
$1/k$	Mean incubation period (days)	5.30	0.23	3.35	0.49
$1/\gamma$	Mean infectious period (days)	5.61	0.19	3.50	0.67

Table 2
Population parameters and estimated R_0 for the Congo 1995 and the Uganda 2000 Ebola outbreaks

Outbreak	Eff. pop. size (N)	Start of interv.	Fatality rate (%)	Estim. R_0	SD R_0
Congo 1995	5,364,500[a]	May 9, 1995 (Khan et al., 1995)	81% (Khan et al., 1995)	1.83	0.06
Uganda 2000	1,867,200[b]	Oct 22, 2000 (WHO, 2001)	53% (WHO, 2001)	1.34	0.03

The post intervention R₀ values were < 1.

What do you think happenned?

The trade-off hypothesis for the evolution of virulence

- **The trade-off hypothesis**: Natural selection should strike an optimal balance between the costs and benefits of harming hosts

- There is a (virulence-related) trade-off between rate of transmission and duration of infection

- A virulent strain of parasite may increase in frequency if, in the process of killing its hosts, it sufficiently increases its chance of being transmitted
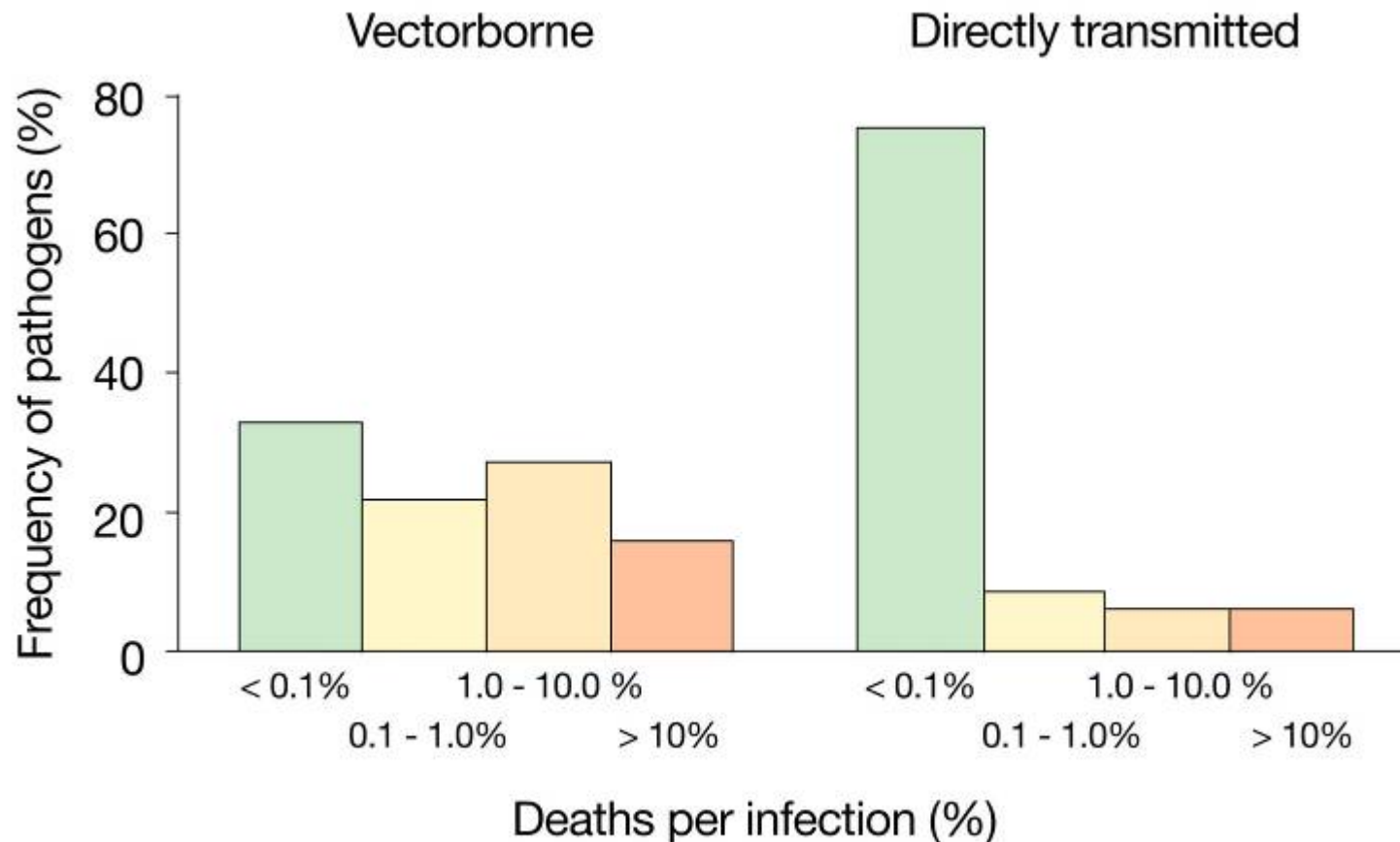
Paul Ewald's view

- Changes in rates of infectious transmission will select for parasite strains or species with different levels of virulence

- Assumes parasite virulence is constrained solely by the need to keep the host alive long enough to facilitate transmission to the next host

- How should this perspective apply to pathogens with different modes of transmission (e.g. direct versus indirect transmission)?

Paul Ewald's view

- All else being equal, vectored diseases ought to have a higher optimal virulence than directly-transmitted ones since immobilizing the host does not prevent (and may even enhance) transmission

- There does seem to be some support for the idea that insect-vectored diseases are more virulent

Different transmission patterns lead to different optimal virulence levels of transmission and virulence are coupled


Vectorborne

Directly transmitted

Frequency of pathogens (%)

Deaths per infection (%)

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Paul Ewald's view

- Diseases that spread by "cultural vectors" should also tend to high virulence.

- **Cultural vectors** are simply amalgams of behavior and environmental conditions that allow immobilized hosts to transmit infections

- Diarrheal pathogens, for example, can be passed through drinking-water systems. An immobilized victim can still infect lots of people if contaminated materials get into drinking water
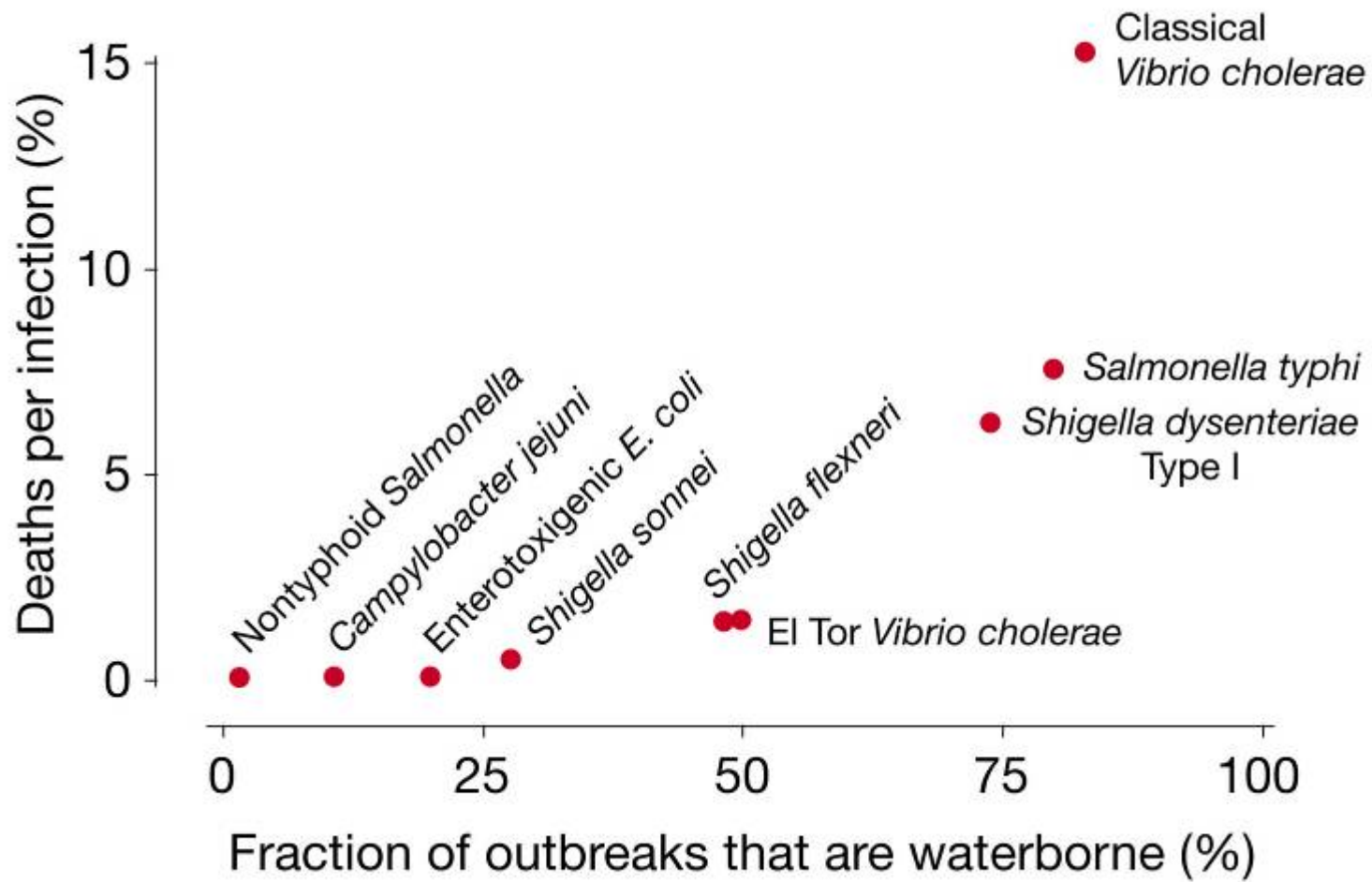
Paul Ewald's view

- So transmission by water may lead to a shift in optimal virulence analagous to insect-vectored transmission

- Again, there is some evidence that is suggestive. For example as water supplies were cleaned up in India in the 1950s and 1960s, a milder form of cholera displaced the more virulent form.

- The problem is that the evidence is almost anecdotal and Ewald advocates on behalf of his favorite theory without considering alternative explanations

Paul Ewald's view

- "Sit-and-wait" pathogens, like *M. tuberculosis* can survive in the external environment for a long, long time.

- How is the cost/benefit calculation affected in such cases?

Paul Ewald's view

- Sexually transmitted diseases can be expected to modulate their virulence in relation to the frequency of sexual activity

- Consider a population of fairly monogamous couples, where, on average, extra pair copulations take place once every three years

- How might this shape the natural history of the parasite?

- How well would a typical cold virus survive if it was being transmitted sexually?

- What might happen if sexual activity increases dramatically?

Paul Ewald's view

- Ewald: "HIV virulence should be correlated with rates of sexual contact….Data gathered over the past decade are consistent with this prediction."

- What data is he referring to?

- Correlation does not imply causation!

Experimental evolution: evolution of virulence

Virulence evolution in a virus obeys a trade-off

Sharon L. Messenger[1]†, Ian J. Molineux[2,3] and J. J. Bull[1,3]*

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- Their experimental system involved *E. coli* as the host and a virus (phage f1) as the pathogen

- Phage f1 produces lasting, non-lethal infections in *E. coli*. but slows growth rate to about one third of normal as it takes over the cellular machinery to make copies of itself (this constitutes its "virulence")

- The phage can be transmitted either horizontally (when secreted virions infect new cells) or vertically (when infected cells divide)

Experimental evolution: evolution of virulence

- The viruses were forced to alternate between the two modes of transmission

- During the vertical phase, secreted virions were prevented from infecting new cells

- During the horizontal phase, secreted virions were harvested and introduced to uninfected bacteria, so the only way they could spread was via secretion

Experimental evolution: evolution of virulence

- One set of cultures had mostly vertical transmission, the other mostly horizontal

- Measured phage virulence (lower growth rate of hosts = higher virulence) and reproductive rate (more rapid secretion of phage = higher reproduction)

Experimental evolution: evolution of virulence

- Prediction 1: correlation between reproduction and virulence. Phages that induced their hosts to secrete more phage would slow the growth of their hosts more severely

- Prediction 2: cultures subjected to long vertical transmission phase would show lower reproduction and lower virulence

- Natural selection should favor strains that allow their hosts to divide more quickly during vertical transmission phase (commensal)

- Natural selection should favor strains that induce host to secrete more virus during horizontal phase (pathogenic)

Experimental evolution: evolution of virulence
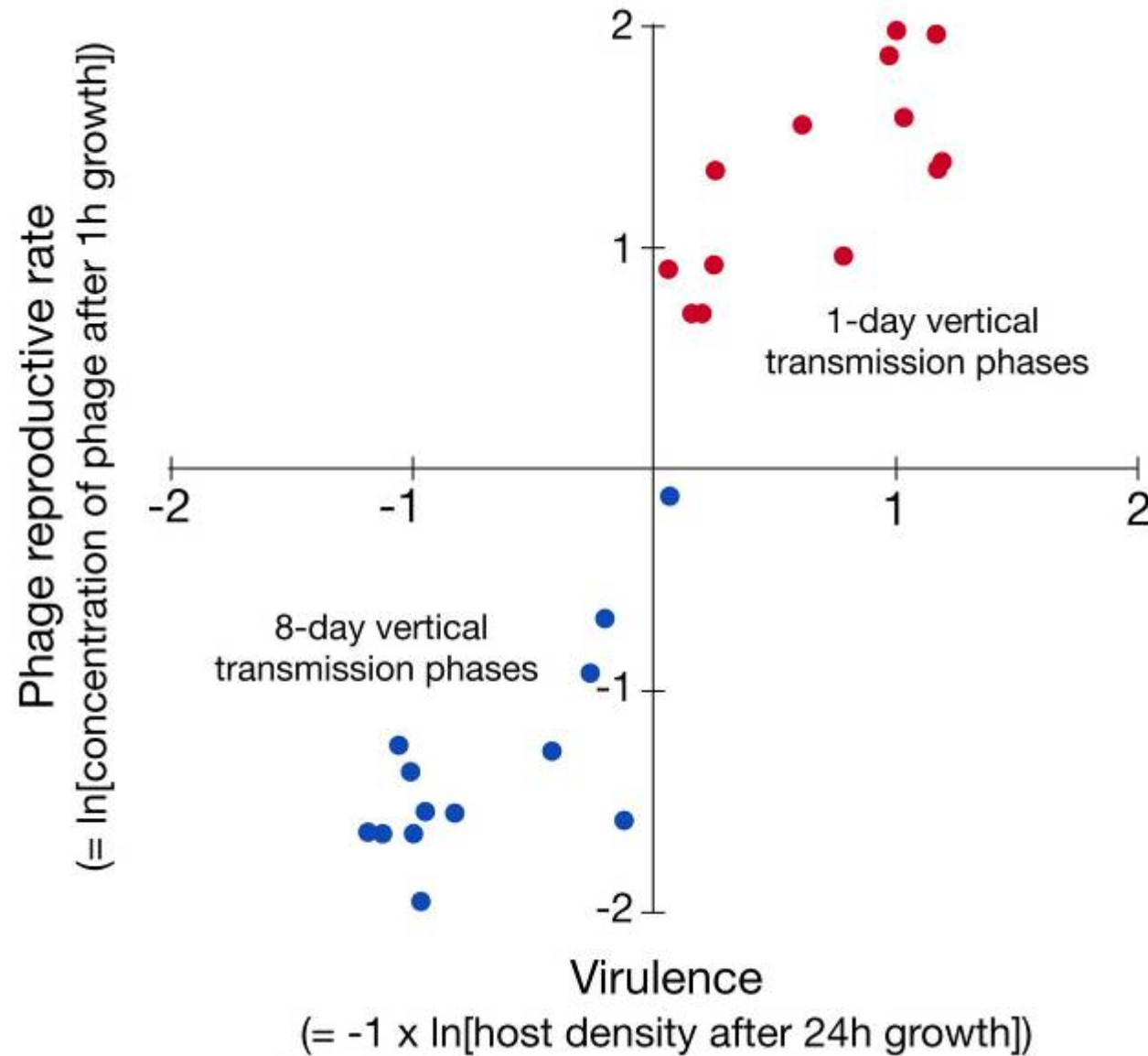
When researchers gave the viruses more opportunities for horizontal transmission (red dots), the viruses evolved higher virulence and higher reproductive rates than predominantly vertically transmitted viruses (blue dots)

Phage reproductive rate (= ln[concentration of phage after 1h growth])

Virulence (= -1 x ln[host density after 24h growth])

1-day vertical transmission phases

8-day vertical transmission phases

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What if increased virulence is not coupled to increased transmission?

- Even when transmission and virulence have no relationship, or a negative relationship, high virulence can be maintained

- According to the **coincidental evolution** hypothesis, the factors responsible for virulence may have evolved for some purpose other than providing a within-host or transmission advantage

- Did botulism toxin really evolve by selection favoring *Clostridium botulinum* bacteria that kill people who eat improperly canned food?

What if increased virulence is not coupled to increased transmission?

- How about *C. tetanae*, a soil bacterium that once in a while colonizes a human host? Are the symptoms of tetanus linked to successful chains of transmission?

- Many symptom-inducing toxins and other virulence determinants may provide no within- or between-hosts advantage

What if increased virulence is not coupled to increased transmission?

- **Short-sighted evolution** is the other way natural selection can favor high virulence, without the virulence being optimized to increase transmission

- Natural selection is a local phenomenon: characters that confer a survival and/or replication advantage on the individual organisms that express them at a given time/environment will be favored

- Whether those temporally/locally favored characters will reduce the fitness of that organism in other times or places is irrelevant

What if increased virulence is not coupled to increased transmission?

- Myopia is a fundamental premise of the theory of evolution by natural selection

- It is also the basis of the short-sighted evolution hypothesis for parasite virulence

- Mutants that are better able to avoid host defenses, or proliferate in the host, or invade new cell/tissue types will have an advantage in the host even if they induce higher virulence that actually reduces the rate of transmission to other hosts

What if increased virulence is not coupled to increased transmission?

- Various agents of meningitis (*Haemopihlus influenzae, Neisseria meningitidus, S. pneumoniae* cause inflammation when they enter the cerebral spinal fluid around the brain

- The invaders have a local, but dead end advantage

- Same with poliovirus

- Same with HIV?

- Others?

- TLR and TNFR - do both of these provide protection against gram-positive bacteria?

- Does the pathway always end in apoptosis?

- CTL Escape (and how it creates cactus like phylogenies?

- Antigenic shift vs. Antigentic drift

- discuss which virulence models will be covered on this exam: I am guessing the trade off model....others?

- am I correct in thinking that we are only have 4 names of import in these
lectures: Ed Hooper, WD Hamilton, and the two Nobel Prize winners whose names
are escaping me right now?