Evolution of Virulence: Malaria, a Case Study
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Lecture outline

- Natural selection on malaria virulence
  - Why are malaria parasites so virulent?
  - Why aren't malaria parasites more virulent?
- Why bother?
  - Possible selective effects of public health interventions
- Other diseases - and a plea

Death or survival

Parasite dose
Parasite genetics
Acquired immunity
Socio-economics
Host genetics

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Malaria parasites in mammalian red blood cells

What selective factors act on parasite virulence?

Benign  Lethal
Parasite virulence spectrum

Pathogen fitness function

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In vitro growth rates of *P. falciparum* from Thai patients


What selective factors act on parasite virulence?
What selective factors favour parasite virulence?

A rodent malaria model: *Plasmodium chabaudi*

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Genetic variation in virulence in *P. chabaudi*

Transmission experiments

Virulent strains transmit better
Genetically diverse malaria infections are the norm....

.... do virulent strains have a competitive advantage in hosts?

Testing outcome of in-host competition

Virulent strains out compete less virulent strains

This is true for across a range of clones
- And it is relative virulence that matters

De Roode, Pansini, Bell, Wargo, Hube, Cheesman, Walliker & Read (2005);
Bell, de Roode, Sim & Read (2006)
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What selective factors act on parasite virulence?

- Enhanced infectiousness
- Within-host competition

Parasite virulence spectrum

Benign → Lethal

What selective factors act on parasite virulence?

- Enhanced infectiousness
- Within-host selection

Parasite virulence spectrum

Benign → Lethal
What is maintaining the virulent Thai parasites?

- They compete better within hosts
- They transmit better to new hosts

Uncomplicated malaria
Severe malaria


What selective factors act on parasite virulence?

- Enhanced infectiousness
- Within-host selection
  - Affected by host immunity?
    - Unaffected
    - Enhanced

Benign → Lethal

Parasite virulence spectrum

What factors select against virulent phenotypes?

- Host death
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What factors select against virulent phenotypes?

- Host death
- Vectors
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Do more virulent clones kill more mosquitoes?

No!

Ferguson, Mackinnon, Chan & Read 2003

What factors select against virulent phenotypes?

- Host death
- Vector death
- Host genetic diversity
- Growth vs. reproduction trade-offs
- Limited by host

What selective factors act on parasite virulence?

- Enhanced infectiousness
- Within-host competition

 Parasite virulence spectrum

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Why bother?

Explain variation in disease pathogenicity in nature

Predict direction of virulence evolution when diseases cross to new hosts

Could some public health programs relax selection against virulence?

How does vaccination change selection on parasite virulence?

- Enhanced infectiousness
- Within-host competition
- Host death

Benign Lethal

Parasite virulence spectrum

Could vaccines weaken selection against virulent pathogens?

Vaccines protect virulent pathogens from themselves

Gandon, Mackinnon, Nee & Read 2001, 2003, 2004

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Vaccination can promote the evolution of virulence by
- Protecting hosts and hence virulent strains
- Increasing in-host competitive advantage of virulence

- Leaky anti-disease vaccines
  may be evolutionary disasters waiting to happen

- Should aim to stop evolution:
  block infection or transmission

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Does virulence evolution occur in response to vaccination?

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Myxoma virus virulence in Australia

Data from Fenner & Fantini 1999
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Human diseases?

Diphtheria - US
Diphtheria incidence, mortality rates, and case-fatality ratio in the United States, 1900 to 1996


Diphtheria - India
Widespread vaccination

Clinical diphtheria in Infectious Diseases Hospital, Delhi, 1954-97
From Singh et al., Epidemiol. Infect. (1999)
Detecting any virulence evolution in human diseases will be a serious challenge

- Case fatality rates change (or don't change) for many reasons
- Problem of common garden
- Need proper molecular epidemiology of virulence determinants

For further reading, see:

Mackinnon, M.J. & Read, A.F. 2004; Virulence in malaria: an evolutionary viewpoint; Philosophical Transactions of the Royal Society of London Biological Sciences; 359: 965-985


All references mentioned in this lecture, and updates, are available on http://readgroup.biology.ac.uk/ or in the references cited therein.