Transmission-virulence trade-offs in malaria parasites

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(References)

- Alizon S, van Baalen M: "Transmission-virulence trade-offs in vector-borne diseases." Theor. Pop. Biol., 2008 (in press)
- Anderson RM, May RM: "Infectious Diseases of Humans." Oxford Univ. Press, 1991.
- Bruce MC, Donnelly CA, Alpers MP, et al.: "Cross-species interactions between malaria parasites in humans." Science, 287: 845-848, 2000.
- Ewald P: "Evolution of Infectious Diseases." Oxford Univ. Press, 1994.
- Knell AJ: "Malaria." Oxford Univ. Press, 1991.

Virulence distribution for direct / indirect transmission diseases (Ewald P, 1994)

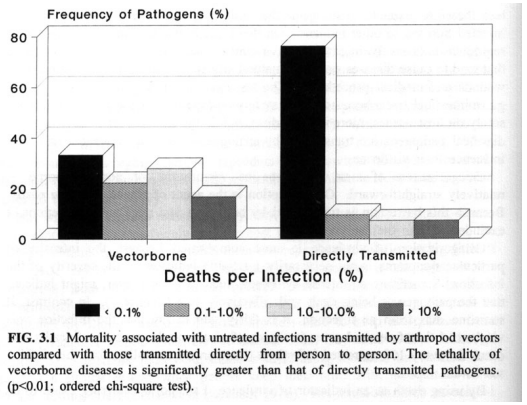


FIG. 3.1 Mortality associated with untreated infections transmitted by arthropod vectors compared with those transmitted directly from person to person. The lethality of vectorborne diseases is significantly greater than that of directly transmitted pathogens. ($p<0.01$; ordered chi-square test).

Introduction

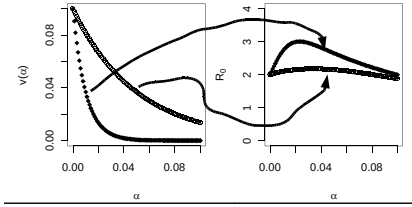
- As Ewald (1994) wrote, most models for the evolution of parasite virulence assuming trade-off between virulence and transmission (weak trade-off for vector-borne diseases).
- There were many criticisms for this assumption's general validity.
  - Parasite reproduction does not necessarily mean virulence.
  - Parasites having sexual life-stage within hosts enables high variability in virulence.
  - Differential host immunization may lead to higher virulence (Gandon, 2004)

Introduction (cont'd)

- There were very few studies to link within-host and epidemiological dynamics of parasites.
- The previous study by the authors showed a trade-off between transmission and virulence emerges from within-host dynamics.
  - The shape of trade-off curve depends on model parameters; it means the existence of "Evolutional Stable Virulence" (=optimal virulence).

Evolution of optimal virulence in single parasite species infection

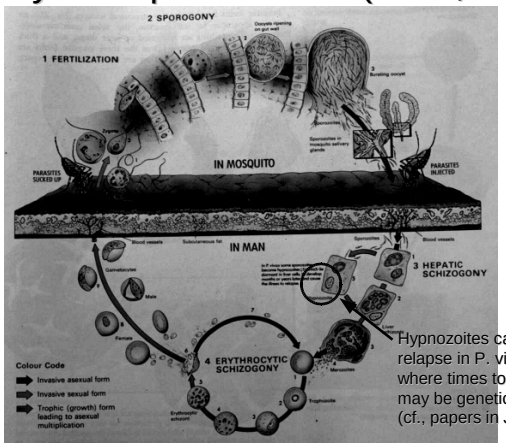
- Using R_0 (basic reproduction number; generally speaking, indicates the number of infected hosts regenerated by the single infectious host), μ (mortality of uninfected host) , α (virulence; excess mortality caused by infection) , ν(α) (recovery rate) , β (transmission rates), and S (density of susceptible hosts), the equation $R_0=\beta S/\{\mu+\alpha+\nu(\alpha)\}$ generally stands (Anderson and May, 1991)



R codes for the previous slide

```
alpha <- seq(0,0.1,length=101)
v1 <- exp(-alpha*20)/10
v2 <- exp(-alpha*100)/10
beta <- rep(0.4,101)
S <- rep(1,101)
mu <- rep(0.1,101)
R0v1 <- beta*S/(mu+alpha+v1)
R0v2 <- beta*S/(mu+alpha+v2)
layout(t(1:2))
par(mar=c(4,4,0.5,0.5),cex=2)
plot(alpha,v1,ylim=c(0,0.1),xlab=expression(alpha),ylab=expres
  sion(paste("v(",alpha,")")))
points(alpha,v2,pch=18)
plot(alpha,R0v1,ylim=c(0,4),xlab=expression(alpha),ylab=expres
  sion(R[0]))
points(alpha,R0v2,pch=18)
```

Life-cycle of plasmodium (Knell, 1991)



Hypnozoites causes relapse in P. vivax, where times to relapse may be genetically fixed. (cf., papers in JID 2007)

Features of P. falciparum

- P.f. kills about 2 million people each year, shares 3.1 % of world mortality.
- Not very virulent, because most adults in endemic area can survive. Majority of malaria death occurs in children due to naive immune system.
- Gametocytes can invade mosquito hosts but it constitutes only a few percent of circulating parasites.

Model

- New features
  - Distinguish two within-host stages (replicate=merozoites=asexual; density x1 / transmit=gametocytes=sexual; density x2)
  - Lymphocytes (density y) kills parasites of both stages
- Equations (see, Table 1)
  - $dx1/dt = (\phi(1-m)-\sigma 1 y)x1$
  - $dx2/dt = \phi m x1-\sigma 2 y x2$
- This framework is applicable to persistent infection (steady state).
  - Old experimental data showed rapid reach to stable state (Boyd, 1949).

Table 1
List of the notations used

Notation	Default value	Description
φ	v	Parasite within-host growth rate
m	v	Parasite conversion rate
x_1	v	Density of asexual parasites
x_2	v	Density of sexual parasites
y	v	Lymphocyte density
σ_1	1	Killing rate of asexual parasites by the lymphocytes
σ_2	0.1	Killing rate of sexual parasites by the lymphocytes
b	0.01	lymphocyte base-line production rate
c_1	0.1	Proliferation rate of lymphocytes activated by asexuals
c_2	0.01	Proliferation rate of lymphocytes activated by sexuals
δ	1	lymphocyte mortality rate
R_0	v	Parasite basic reproduction ratio
α	v	Virulence, i.e. infected host mortality due to the infection
β	v	Transmission rate of the parasite
γ	v	Host recovery
S	v	Density of susceptible hosts
α	10	Transmission constant
M	v	Number of sexual parasites in a mosquito blood-meal
μ	0.1	Host natural death rate
u_1	0.05	Deleterious effect of a asexual (replicating) parasites
u_2	0.05	Deleterious effect of a sexual (non-replicating) parasites
w	0.01	Lymphocyte detrimental effect

Variables are indicated with a v and constants are indicated by their default values.

Model of immune system

- Strength of immune system = lymphocyte density y (not constant)
- Equation
  - dy/dt = b + c1x1 + c2x2 – δy
    - b: baseline production rate of lymphocyte
    - c1, c2: increase of lymphocytes production by merozoites and gametocytes, respectively.
    - δ: lymphocyte mortality

Within-host stable state

$$\tilde{x_1}(\varphi, m) = \frac{\sigma_2}{\sigma_1} \frac{(1-m)\,\delta\,\varphi - b\sigma_1}{c_2\sigma_1 m - (1-m)c_1\sigma_2}(1-m)$$

$$\tilde{x_2}(\varphi, m) = \frac{(1-m)\delta\,\varphi - b\,\sigma_1}{c_2\sigma_1 m - (1-m)c_1\sigma_2} m$$

$$\tilde{y}(\varphi, m) = \frac{1-m}{\sigma_1}\varphi.$$

- These can be derived from the equations when differentials (increase rates) are zero.

Epidemiological dynamics

- As already shown, basic reproduction number R_0 is (let β transmission rate, μ natural mortality, α excess mortality due to parasites, γ recovery rates, S susceptible hosts density), $R_0 = \beta S / (\mu + \alpha + \gamma)$.
- Considering two host species, R_0 should be the products of R_0's for two hosts.
- But by assuming vectors' R_0 as constant,

$$R_0 \propto \frac{\beta_{h\to v}}{\mu_h + \alpha_h + \nu_h} S_h.$$

Epidemiological dynamics (cont'd)

- Transmission from human to vector can be linked with stable density of sexual stage parasites ($\tilde{x}2$).
- Since mosquitoes have immune system, minimum number of sexual parasites is needed to infect.
- Assume a mosquito ingests 4 microlitter out of 5 litter human blood pool, mean number of sexual parasites within it (M) is, using stable density, $M = 8 \times 10^{-7}\,\tilde{x}2$.
- Probability of having exactly n sexual parasites ($p_n(M)$) obeys Poisson distribution, thus $p_n(M) = M^n e^{-M} / n!$
- β is the products of $p_n(M)$ and a transmission constant, and assume the parasite virulence as, $\alpha(\varphi, m) = u_1\,\varphi\tilde{x}_1(\varphi, m) + u_2\,\tilde{x}_2(\varphi, m) + w\,\tilde{y}(\varphi, m).$

$$R_0(\varphi, m) \propto \frac{aP_n\,(8\times 10^{-7}\,\tilde{x}_2(\varphi, m))}{\mu_h + u_1\varphi\tilde{x}_1(\varphi, m) + u_2\tilde{x}_2(\varphi, m) + w\tilde{y}(\varphi, m)} S_h$$

Results

- Transmission rate has S-shape (Fig.1)
  --> exisntence of infective threshold
- Trade-offs between transmission and virulence (Fig.2)

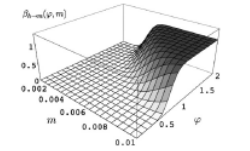


Fig. 1. Transmission rate of the parasite from its main host to the mosquito. The transmission function has a S-shape: at low sexual parasite densities the transmission is complicated and at high densities it saturates. Parameter values are $\alpha = 40, \varepsilon_1 = 0.1, \varepsilon_2 = 0.01, \alpha_1 = 1, \alpha_2 = 0.1, \nu = 0.01, \delta = 1, \bar{a} = 10$.

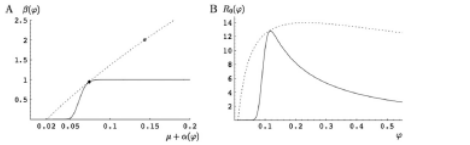


Fig. 2. Trade-off curve (A) and basic reproduction ratio curve (B). Dashed lines show the same functions assuming a linear transmission rate. On figure A, the black dot indicates the ESV of the plain curve and the grey dot indicates the ESV of the dashed curve. Parameter values are identical to Fig. 1 and $\mu = 0.1, \alpha_1 = 0.05, \alpha_2 = 0.05$ and $w = 0.01$.

Results (cont'd)

- Sensitivity analysis for host natural mortality changes (Fig.3); A for linear, B for sigmoid transmission function; μ's effects are larger in B than in A.
- Effect of parasite conversion rate (m) and within-host growth rate (ϕ) on R_0 (Fig.4)

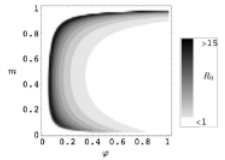


Fig. 4. Effect of the parasite conversion rate (m) and of the within-host growth rate (φ) on the R_0 value. Areas where the parasite's R_0 is greater than unity are coloured in black. Note that if $m \approx 1$ or if φ is small compared to m, our results are not valid anymore (cf. the black crescent area). The darker the area, the higher the R_0. Parameter values are that of Fig. 2.

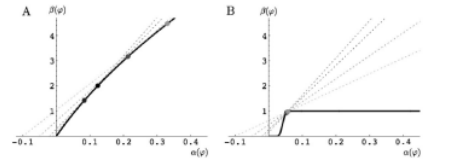


Fig. 3. Effect of host natural mortality (μ) on the trade-off curves (A) for a linear transmission function and (B) for a sigmoid transmission function. ESV are indicated by a large dot. Dashed lines are the tangent to the curves for various values of μ. Parameter values are identical to Fig. 2. In green $\mu = 0.1$, in red $\mu = 0.05$, in black $\mu = 0.02$ and in blue $\mu = 0.01$. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Implication to health policy

$$\frac{dx_1}{dt} = (\varphi(1-m) - \sigma_1 y - \tau_1)\,x_1$$

$$\frac{dx_2}{dt} = m\,\varphi x_1 - (\sigma_2 y + \tau_2)x_2$$

- Effect of a treatment targeting either the asexual (A; $\tau 1$) or sexual (B; $\tau 2$) life stage of parasites (Fig.5)
  --> Increasing $\tau 2$ has clear impact.

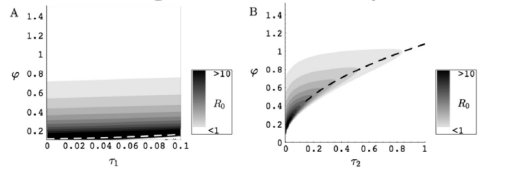


Fig. 5. Effect of a treatment targeting either the asexual (A) or the sexual life-stage (B). Grey colours indicate the value of the R_0 (the darker the area, the greater the R_0) depending on the intensity of the treatment and on the parasite growth rate (φ). The black and white dashed lines indicate the optimal value of φ for a given treatment intensity. In the white areas, the parasite cannot survive in the host population (i.e. $R_0 < 1$). Parameter values are identical to Fig. 2.

Change of dominant plasmodia in Solomon Islands

Timing	Nov. 1995			Feb. 2006			Sep. 2006		
Age class	P.f.	P.v.	Total	P.f.	P.v.	Total	P.f.	P.v.	Total
0-10	23	8	34/95	13	29	44/105	8	21	29/70
11-20	6	1	8/21	3	5	8/17	6	4	11/56
21-30	3	0	3/12	3	1	4/16	1	4	5/24
31-40	2	3	5/22	6	1	7/36	2	4	6/32
41-50	1	1	2/11	2	3	5/13	0	2	2/16
51-	2	0	2/25	2	0	2/29	2	1	3/25

Timing	Feb. 2007			Sep. 2007			Feb. 2008		
Age class	P.f.	P.v.	Total	P.f.	P.v.	Total	P.f.	P.v.	Total
0-10	5	8	13/53	6	9	15/59	5	8	13/64
11-20	1	3	4/12	2	5	7/22	1	2	4/22
21-30	1	1	2/11	1	2	3/17	2	0	2/23
31-40	0	0	0/21	1	2	3/19	1	3	4/18
41-50	0	1	1/9	1	0	1/9	0	1	1/8
51-	0	0	0/15	1	0	1/20	0	0	0/19

Implications for my study

- In Solomon Islands, dominant parasites changed from P.f. to P.v. for recent 10 years.
- Parasite rates of P.f. decreased under chloroquine treatment and wide-use of bednets.
- Instead, asymptomatic P.v. infection increased.
- Replication of plasmodia is restricted by the existence of other species/strains (Bruce et al., 2000)
- Switching of dominant plasmodium species in Solomon Islands could be modeled as application of this virulence evolution models?