Conceptual aspects in the elimination of vector-borne diseases

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Control of vector-borne diseases

Onchocerciasis: Vectorcontrol until 2002, successor program: mass drug administration of ivermectin

Onchocerciasis Control Programme

1975 - 2000

African Programme for Onchocerciasis Control (APOC)

Lymphatic filariasis: Elimination intended by mass drug administration of ivermectin / DEC ...

Global Program to Eliminate lymphatic filariasis (GPELF)

http://apps.who.int/tdr/
Example: onchocerciasis in Africa
Data ... leading to concepts

[Graphs showing data trends related to nematode infection rates and egg outputs across different conditions.]
Elimination thresholds for vector-borne diseases

- Infection cannot persist: Elimination is possible.
- Infection can persist, elimination is possible.
- Infection persists, elimination is difficult.

**Graph:***
- **Y-axis:** Parasite density [parasites/host]
- **X-axis:** Annual Biting Rate (ABR) [bloodmeals/year · host]

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*Review*  
*TRENDS in Parasitology*  
Vol.21 No.2 February 2005
Vector-related threshold: Threshold biting rate

"If there are too few vector-host contacts, then, a parasite in the human host will die before the next one can establish"
Control of vectors

If the intervention does not reach the threshold biting rate, the parasite population will re-establish at its pre-control equilibrium.

If the intervention reaches the threshold biting rate, the parasite population dies out without further interventions.

Parasites [ host ]

Annual Biting Rate (ABR) \[ \frac{\text{bloodmeals}}{\text{year} \cdot \text{host}} \]
Parasite-related thresholds: breakpoints

"If there are too few parasites in a host, then, mating is not possible and reproduction cannot occur"
Reason for breakpoints: Mating of dioecious parasites

\[ P(2\text{sex}) = 1 - P(\text{only male worms}) - P(\text{only female worms}) \]
\[ = 1 - 0.5^{\text{males}} - 0.5^{\text{females}} \quad // \text{males} \equiv \text{females} = W \]
\[ = 1 - 0.5^{W-1} \]

\[ W \sim \text{NBD}(\bar{w}, k): \]
\[ \varphi(\bar{w}) = \sum_{W=1}^{\infty} \left(1 - 0.5^{W-1}\right) \cdot \text{NBD}(\bar{w}, k) \]
\[ = 1 + \left(\frac{k}{k + \bar{w}}\right)^k - 2^{k+1} \left(\frac{k}{2k + \bar{w}}\right)^k \]

Control of parasites

Below a breakpoint, the parasite population dies out without further interventions.

If the intervention does not reduce the parasite population below a breakpoint, it will re-establish at its pre-control equilibrium.

Annual Biting Rate (ABR) \[ \frac{\text{bloodmeals}}{\text{year} \cdot \text{host}} \]
Evaluating thresholds by simulation

Average no. of adult female 
O. volvulus per person

Pre-control

Control by microfilaricide

Post-control

W Equilibrium parasite burden
BP Breakpoint
E Elimination achieved
Density-dependent regulation in a host-parasite relationship

- Limitation (negative feedback)
- Facilitation (positive feedback)
- No regulation

No. of parasites in the vector

No. of parasites in the human host

Number of parasites of stage x
Density-dependent processes:

**Limitation**

**Facilitation**
Density-dependent processes modifying eradicability

Facilitation "facilitates" the eradicability of an infection, whereas limitation "limits" the prospects of eradication.
Comparing processes of density-dependent regulation

- No. of parasites in the human host: $n_1$
- No. of parasites in the vector: $n_4$
- Equilibrium parasite burden

Diagram:
- $n_x$: No. of parasites
- $n_{x+i}$: Density-dependent regulation
- $n_2$: No. of parasites in the human host
- $n_3$: No. of parasites in the vector
- $n_5$: Equilibrium parasite burden
- $n_6$: Density-dependent regulation
Equilibrium under limitation

- **h**: No. of parasites in the human host
- **v**: No. of parasites in the vector

Graphs showing:
- **h(v)**: Equilibrium parasite density
- **v(h)**: Unstable zero

Equilibrium parasite density

**Unstable zero**
### Equilibria under facilitation

<table>
<thead>
<tr>
<th>No. of parasites in the vector</th>
<th>No. of parasites in the human host</th>
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<tbody>
<tr>
<td>Stable equilibrium</td>
<td>Stable equilibrium</td>
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<tr>
<td>Unstable equilibrium</td>
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<tr>
<td>Stable zero</td>
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</tbody>
</table>

- $h$: No. of parasites in the vector
- $v$: No. of parasites in the human host
- $h(v)$: Function of parasites in the vector
- $v(h)$: Function of parasites in the human host

![Diagram showing equilibria under facilitation](attachment:image.png)
Model (filarial parasites)

Acquisition & survival of adult parasites:
\[
\frac{dw}{dt} = \lambda(w, ATP) - (\sigma_w + \mu)w
\]
- Acquisition rate
- Mortality of adult worms + humans

Production & survival of microfilariae:
\[
\frac{dm}{dt} = \phi(w) \beta(w) - (\sigma_m + \mu)m
\]
- Mating probability
- Rate of microfilarial production
- Mortality of adult worms + humans

Larval development in flies (assumed to be at equilibrium):
\[
l(m) = \frac{c_1 m}{1 + c_2 m}
\]

Annual Transmission Potential:
\[
ATP = \varepsilon ABR \cdot \frac{l}{l^*}
\]
- Annual Biting Rate
- Adjustment to provide comparable equilibriae
Which model to take?

Parasite distributions often cannot be adequately characterized by the mean only:

In a finite world, limitation is the rule:

Deterministic model
- **generality**
- **understanding** Biology of disease
- Heterogeneities among parasites, vectors & hosts
- Discrete & limited distributions

Stochastic model
- **predicting** Intervention success
- **realism**

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Ingested $m_i$ per fly

Rel. frequency

Stage before $m_i$
Attempt: stochastic with deterministic properties

Number of hosts $H_{v,w}$ with $v$ premature (developing L4) and $w$ mature worms (adult worms).

$v^+$: maximum no. of premature worms in the host
$w^+$: maximum no. of mature worms in the host

$H_0,0 \xrightarrow{\sigma_H} H_0,1 \xrightarrow{\sigma_W} H_1,0 \xrightarrow{\sigma_W} H_1,0$ (L4 mature to adult worms within 1 year)

 Parasites are acquired at rate $\Lambda$, depending on
- $u$: the no. of L3 released per bite
- $v$: the no. of L4 in the host
- $w$: the no. of adult worms in the host

$\Lambda^u_{v,w}$

$u^+$: maximum no. of L3 that a bite can contain. We assume: $u_{max} < v_{max}$
Acquisition, maturation & death of parasites

No. of adult worms \([0…w^+ = 200]\)

No. of immature worms \([0…v^+ = 10]\)

\[\Lambda^i_{v, w}\]

\[\mu_H\]

\[\sigma_H\]

\[1\sigma_W\]

\[2\sigma_W\]

\[1\mu_W\]

\[2\mu_W\]

\[10\mu_W\]
Acquisition & death of parasites: model

\[ \frac{dH_{v,w}}{dt} = \]

- \( \sigma_H H_{v,w} \) \text{ Hosts die} \\
- \( w \sigma_w H_{v,w} \) \\
+ \( (w+1) \sigma_w H_{v,w+1} \) \text{ Parasites die} \\
- \( \sum_{u=1}^{u^+} H_{v,w} \Lambda^u_{v,w} \) \text{ Parasites acquired} \\
+ \( \sum_{i=\text{Max}(0,v-u^+)}^{v-1} H_{i,w} \Lambda^{v-i}_{i,w} \) \\
- \( v \mu_v H_{v,w} \) \\
+ \( (v+1) \mu_v H_{v+1,w-1} \) \text{ Parasites mature}
Frequency of people with $w$ adult worms

\[
H_w = \sum_{v=0}^{v^+} H_{v,w}
\]
Microfilaria production: $w \rightarrow m_s$

The microfilarial density $m_s$ is beta-binomial distributed with expectation $p_m \cdot m^+$ and a dispersion parameter $\beta$

$w$ is the number of adult worms per person, $m_s$ is the number of microfilariae per mg skin snip, and $m^+$ is the maximum number of microfilariae which can be found in a skin snip.

$$p_m = \frac{b \cdot w}{1 + b \cdot w}$$

$$m_s(w) = p_m \cdot m^+$$

$b = 0.1 \in [0.0 \ldots 10.0]$, $\beta = 2.0 \in [0.01 \ldots 100.0]$, $m^+ = 500.0 \in [10.0 \ldots 10000.0]$
MF ingested: $m_s \rightarrow m_i$

The log of microfilarial intake $m_i$ is betabinomial-distributed, with expectation $\mu$, Min, Max proportional to the log of $m_s$:

$$\log(m_i + 1) = y_0 + s \log(m_s + 1)$$

**Expectation**: $\mu = 10^{y_0} (m_s + 1)^s - 1$

**Minimum**: $m_{i,\text{min}} = \text{Max}[10^{y_0-\Delta}(m_s + 1)^s - 1, 0]$

**Maximum**: $m_{i,\text{max}} = 10^{y_0+\Delta}(m_s + 1)^s - 1$

$s = 0.62 \in [0.0...5.0], \; \beta = 22.2 \in [0.01...1000.0], \; y_0 = 0.38 \in [0.0...10.0]$

Prevalence of infected flies: 99%
Fitting the model to data