Control and elimination of vector-borne diseases: Thresholds, breakpoints & strategies

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International Conference on Mathematical and Theoretical Biology, Pune, 23-27 January, 2012
Overview

• **Neglected tropical diseases**: Research questions, problems & modelling

• **Modelling vector-borne diseases**: Transmission threshold
  in the example of *micro* parasites / deterministic model: Visceral Leishmaniasis, Indian subcontinent

• **Non-linearities**: Breakpoints & density-dependence
  in the example of *macro* parasites / stochastic model: Onchocerciasis, Africa

• **Interventions & elimination**
  from the perspective of transmission thresholds & breakpoints

• **Interventions suffering from 'chain limitation'**
Control of vector-borne diseases

Common interventions:
- Treatment of humans
- Control of vectors

$s_1$ to $s_4$: developmental stages of the parasite
"... It is of course desirable to work with manageable models which maximize generality, realism and precision toward the overlapping but not identical goals of understanding, predicting, and modifying nature. But this cannot be done. ..."
Aim: determination of thresholds

Parasite density (Parasites/Host)

Infection cannot persist

Infection can persist, elimination is possible

Infection persists, elimination is difficult

Annual biting rate (ABR) (Bloodmeals/Year · Host)
Example 'micro'parasites: Leishmaniasis

- Protozoa, Flagellata, Trypanosomatida
- Vector: Sandflies (Phlebotomus)
- 'Kala Azar', lethal
Visceral Leishmaniasis: deterministic model

Model prediction: transmission threshold

- **Model prediction**: An endemic state is not expected if flies take on average less than about two bloodmeals per person and day.

- **Prevalence data**: about 12% of the population infected, with the majority of humans showing no symptoms (asymptomatic infections).

- **Elimination by vector control**: if the vector population (in this region) can be reduced by factor 3 to 4.

Limitations of the deterministic model: assumptions on infinite population size, homogenous mixing, etc., thus not (yet) considering factors like clusters (villages), seasonal transmission, stochastic extinction, etc.
Example 'macro'parasites: Onchocerciasis

- Helminths ('Worms': are countable)
- Vector: Blackflies (*Simulium*)
- 15 Mio. infected, 120 Mio. at risk
- Worst outcome: blindness ('river blindness')

![Geographic distribution of Onchocerciasis](image)
Wishes, demands & constrictions

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

In a finite world, limitation is the rule:

Deterministic model
- **generality**

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

**Biology of disease**

Heterogeneities among parasites, vectors & hosts

Discrete & limited distributions

**Rel. frequency**

Ingested $m_i$ per fly

Ingested $m_i$ per fly

Stage before $m_i$
Attempt: stochastic with deterministic properties

\[ H_{v,w} \]

Number of hosts 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

- Hosts are born
- 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

- Worms die
- L4 mature to adult worms within 1 year
- Hosts die

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

Assumption: Hosts cannot harbour more than 10 immature worms at the same time.
Acquisition & death of parasites: model

\[
\frac{dH_{v,w}}{dt} = -\sigma_H H_{v,w} \quad \text{Hosts die}
\]

\[
- w\sigma_w H_{v,w} + (w+1)\sigma_w H_{v,w+1} \quad \text{Parasites die}
\]

\[
- \sum_{u=1}^{u^+} H_{v,w} \Lambda_{v,w}^u + \sum_{i=\text{Max}(0,v-u^+)}^{v-1} H_{i,w} \Lambda_{i,w}^{v-i} \quad \text{Parasites acquired}
\]

\[
- \nu \mu_v H_{v,w} + (v+1)\mu_v H_{v+1,w-1} \quad \text{Parasites mature}
\]
## What type of model is this?

<table>
<thead>
<tr>
<th>Property</th>
<th>Model type</th>
</tr>
</thead>
<tbody>
<tr>
<td>Same initial conditions → same output</td>
<td>Deterministic</td>
</tr>
<tr>
<td><em>Distributions</em> are modelled, not <em>means</em></td>
<td>Stochastic</td>
</tr>
<tr>
<td>The model is based on transition <em>rates</em>, not on transition <em>probabilities</em></td>
<td>Deterministic</td>
</tr>
<tr>
<td>The model assumes infinite population size</td>
<td>Rather deterministic</td>
</tr>
</tbody>
</table>

My suggestion: "Stochastically structured deterministic model"
Frequency of people with \( w \) adult worms

\[
H_w = \sum_{\nu=0}^{\nu^+} H_{\nu, w}
\]

Rel. frequency

\( w \) adult worms per person
Deterministic' redistribution of parasite numbers in the life-cycle
(here: stage before transmission: $s_1=w$, $s_2=m_s'$)

Data-based Distribution of $m_s$ conditional on $w$

Weighting with distribution of $w$

2-dimensional distribution

Marginal distribution

Distribution of $m_s$
'Deterministic' redistribution of parasite numbers in the life-cycle
(here: stage at transmission: $s_2 = 'm_s', s_3 = 'm_i'$)

Prevalence of infected flies: 99%

Data-based Distribution of $m_i$ conditional on $m_s$
Fitting the model to data

Elimination thresholds for vector-borne diseases

- **Parasite density [parasites/host]**
  - Infection cannot persist
  - Infection can persist, elimination is possible
  - Infection persists, elimination is difficult

- **Annual Biting Rate (ABR) [bloodmeals/year/host]**
Vector-related threshold: Threshold biting rate

If vector control under-runs the threshold biting rate, the parasite population dies out without further interventions.

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

Annual Biting Rate (ABR) [bloodmeals/year · host]
Parasite-related thresholds: breakpoints

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.

Infection cannot persist → elimination is possible

Infection persists → elimination is difficult

Annual Biting Rate (ABR) \[ \frac{\text{bloodmeals}}{\text{year} \cdot \text{host}} \]
Vector-host contacts (bloodmeals/year)

0.1

1

0.5

0.2

10

5

3

1,000 10,000

3,000

Parasite density in humans

Persistence graph

Vector-host contacts (bloodmeals/year)

Parasite density in humans
Endemic parasite burden

Parasite density in humans

Vector-host contacts (bloodmeals/year)
Vector-host contacts (bloodmeals/year)

Parasite density in humans

Breakpoints

Vector-host contacts (bloodmeals/year)
Vector-host contacts (bloodmeals/year)

Parasite density in humans

Endemic states

Endemic
Vector-host contacts (bloodmeals/year)

Parasite density in humans

Non-endemic states

endemic

Non-endemic
Vector-host contacts (bloodmeals/year)

- 0.1
- 1
- 0.5
- 0.2
- 10
- 5
- 3

Parasite density in humans

- Sub-critical transmission
- Endemic
- Non-endemic
- Sub-critical
Vector-host contacts (bloodmeals/year)
Vector-host contacts (bloodmeals/year)

0.1  1  0.5  0.2

10  5  3

1,000  10,000  3,000

Parasite density in humans

Threshold biting rate TBR

Endemic

Sub-critical

Infection-free

Non-endemic

Vector-host contacts (bloodmeals/year)
Two villages

Parasite density in humans

Vector-host contacts (bloodmeals/year)
Vector-host contacts (bloodmeals/year)

Parasite density in humans

Village A (ABR=2000)
Vector-host contacts (bloodmeals/year)

Parasite density in humans

TBR

A

B

1,000 10,000 3,000
Vector-host contacts (bloodmeals/year)

Parasite density in humans

Years

Vector-host contacts (bloodmeals/year)
Vector-host contacts (bloodmeals/year)

Parasite density in humans

TBR

CDTI
No control

A
B

Years

0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15

Vector-host contacts (bloodmeals/year)

1,000 10,000

3,000
Vector-host contacts (bloodmeals/year)

Parasite density in humans

CDTI
No control

A
B

TBR

Years

Vector-host contacts (bloodmeals/year)

0 1 2 3 4 5 6 7 8 9 10

11 12 13

14

15

0.1

0.5

0.2

1

1,000 10,000 3,000
Vector-host contacts (bloodmeals/year)

Parasite density in humans

CDTI
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1,000 10,000 3,000
Vector-host contacts (bloodmeals/year)

Parasite density in humans

Years

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No control

A

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TBR

1,000

3,000

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Parasite density in humans

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Vector-host contacts (bloodmeals/year)
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TBR

1,000 3,000 10,000

0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15

0 0.1 0.2 0.5 1

0.1 1 10

1,000 10,000 3,000
Vector-host contacts (bloodmeals/year)

Parasite density in humans

Years

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No control

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TBR

0.1
0.2
0.5
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3
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10
3,000
10,000
1,000

Vector-host contacts (bloodmeals/year)
Vector-host contacts (bloodmeals/year)

Parasite density in humans

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Years

1,000 10,000 3,000

0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15

Vector-host contacts (bloodmeals/year)
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Parasite density in humans

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1,000 10,000 3,000 10

0.1 0.2 0.5 1
Vector-host contacts (bloodmeals/year)

Parasite density in humans

Years

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TBR

1,000 10,000 3,000

0 0.1 0.2 0.5 1 10
Vector-host contacts (bloodmeals/year)

Parasite density in humans

Years

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0 1 2 3 4 5 6 7 8 9 10

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Vector-host contacts (bloodmeals/year)

Parasite density in humans

Years

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TBR

A

B

1,000

3,000

10,000

Vector-host contacts (bloodmeals/year)

10

5

3

1

0.5

0.2

0.1

0.01
Vector-host contacts (bloodmeals/year)

Parasite density in humans

Years

CDTI

No control

B

A

TBR

1,000 10,000

3,000

0.1

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5

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Vector-host contacts (bloodmeals/year)

Parasite density in humans

Years

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Parasite density in humans

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Years

0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15

0 1 2 3 4 5 6 7 8 9 10

1,000 10,000 3,000

Years
Vector-host contacts (bloodmeals/year)

Parasite density in humans

Years

CDTI

No control

Vector-host contacts (bloodmeals/year)

Parasite density in humans

TBR

A

B
Vector-host contacts (bloodmeals/year)

Parasite density in humans

Years

CDTI

No control

Years

TBR

Vector-host contacts (bloodmeals/year)
Termination of CDTI

Vector-host contacts (bloodmeals/year)

Parasite density in humans

Termination of CDTI
Vector-host contacts (bloodmeals/year)

Parasite density in humans

CDTI
No control

A
B
TBR

Years

Vector-host contacts (bloodmeals/year)
Vector-host contacts (bloodmeals/year)

Parasite density in humans

Years

CDTI
No control

Vector-host contacts (bloodmeals/year)
Vector-host contacts (bloodmeals/year)

Parasite density in humans

Years

CDTI

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TBR

A

B

0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15

0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15

10,000 3,000 1,000
Vector-host contacts (bloodmeals/year)

Parasite density in humans

CDTI
No control

B

A

TBR

Years

Vector-host contacts (bloodmeals/year)

0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15
Vector-host contacts (bloodmeals/year)

Parasite density in humans

Years

CDTI

No control

B

A

TBR

1,000 10,000

3,000

Vector-host contacts (bloodmeals/year)
Vector-host contacts (bloodmeals/year)

Parasite density in humans

Years

CDTI

No control

TBR

A

B

0

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12

13

14

15

1,000

3,000

5,000

10,000
Vector-host contacts (bloodmeals/year)

Parasite density in humans

Years

CDTI

No control

A

B

TBR

1,000 10,000 3,000
Vector-host contacts (bloodmeals/year)

Parasite density in humans

Years

CDTI
No control

B
A

TBR

1,000 10,000 3,000

0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15

0 1 2 3 4 5 6 7 8 9 10

0.1
Vector-host contacts (bloodmeals/year)

Parasite density in humans

CDTI
No control

B
A

Years

0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15

Parasite density in humans

Vector-host contacts (bloodmeals/year)

TBR
Vector-host contacts (bloodmeals/year)

Parasite density in humans

CDTI

No control

TBR

A

B

0
1
2
3
4
5
6
7
8
9
10
11
12
13
14
15

Years

Vector-host contacts (bloodmeals/year)
Vector-host contacts (bloodmeals/year)

Parasite density in humans

Years

CDTI
No control

TBR

A

B

1,000 3,000 10,000

0.2 0.1 0.01
Vector-host contacts (bloodmeals/year)

Parasite density in humans

CDTI

No control

Years

0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15

1,000 10,000 3,000

TBR

A

B

Vector-host contacts (bloodmeals/year)
Vector-host contacts (bloodmeals/year)

Parasite density in humans

CDTI

No control

TBR

Years

0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15

A

B

1,000 10,000

3,000
Vector-host contacts (bloodmeals/year)

Parasite density in humans

Years

CDTI
No control

TBR

B

A

1,000 10,000 3,000
Vector-host contacts (bloodmeals/year)

Parasite density in humans

Years

CDTI

No control

TBR

A

B

1,000 10,000

3,000

10

0.2

0.5

1

3

5

10

Vector-host contacts (bloodmeals/year)
Vector-host contacts (bloodmeals/year)

Parasite density in humans

Years

CDTI

No control

Elimination

TBR

A

B

Vector-host contacts (bloodmeals/year)
Vector-host contacts (bloodmeals/year)

Parasite density in humans

Years

CDTI

No control

Elimination

Relapse

A

B

TBR

0  1  2  3  4  5  6  7  8  9  10

11  12  13  14  15

0  0.1  0.2  0.5  1  3  5  10

1,000  3,000  10,000

Vector-host contacts (bloodmeals/year)
Non-linearities & thresholds

• Non-linearities:
  – e.g. density-dependence: if the parasite induces an immuno-suppression, host properties like the immunological responsiveness can depend on the number of parasites in the host. Such processes can feedback negatively or positively.

• Two types:
  – Limitation processes (negative feedback mechanisms) limit chances to eliminate the parasite
  – Facilitation processes (positive feedback mechanisms) facilitate changes to eliminate the parasite
Density-dependent regulation in a host-parasite relationship

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

Number of parasites of stage x

No. of parasites in the human host

No. of parasites in the vector

- $n_1$, $n_2$, $n_3$, $n_4$, $n_5$, $n_6$
Density-dependent processes modifying eradicability

Facilitation "facilitates" the eradicability of an infection, whereas limitation "limits" the prospects of elimination.
Interventions under chain limitation

Life cycle stages $s_1$, $s_2$, $s_3$, $s_4$:

Chain limitation:

- Equilibrium before intervention
- Equilibrium after intervention
Conclusions

• Deterministic models are not necessarily bad, or too simple. At least in the case of microparasitic infections they may remain the better tool when *understanding* stands in the foreground.

• Stochastic models or hybrid approaches are worth to be considered when macroparasitic infections are to be studied. Advantages when fitting the model to data can recompense higher modelling efforts.

• Two types of thresholds determine the eradicability of a vector-borne disease: transmission thresholds and breakpoints.

• Non-linearities and feedback mechanisms like density-dependence can substantially impact on the value of a threshold.

• 'Chain limitation' is a very potent mechanism to stabilize the persistence of pathogens in host populations
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http://www.uni-tuebingen.de/modeling/Mod_Duerr_Intro_en.html
Abstract

Control and elimination of vector-borne diseases: thresholds, breakpoints and strategies

Vector-borne diseases receive increased attention since terms like ‘neglected tropical diseases’ have been established. The two major strategies to control these infections are vector control and treatment of humans. Mathematical models to describe transmission and control of these infections must consider the role of the vectors as these act as ‘engine’ of transmission.

The chances for successfully eliminating these infections depend largely on the roles of the vectors, and they can be substantially altered by non-linear or density-dependent functions linking the transmission between vectors and definite hosts, or, regulating the parasite’s persistence within these hosts.

Two types of thresholds determine the elimination profile of a parasite: transmission thresholds (vector density below which the infection cannot persist) and breakpoints (parasite density below which the infection cannot persist).

These two measures can be best illustrated by persistence graphs showing the average number of parasites per human host (or other host populations) dependent on the average number of vectors per definite host (often called biting rate when flies are vectors).

In this talk, concepts of persistence, control and elimination of parasites are illustrated together with the concepts of transmission thresholds and breakpoints in the examples of two indirectly transmitted diseases, i. e. the microparasitic infection visceral leishmaniasis (‘Kala Azar’) in the Indian subcontinent and the macroparasitic infection onchocerciasis (‘river blindness’) in Africa. Limitations of simple deterministic modeling approaches are discussed, and options for stochastic models approaching the master equation are shown.