MODELING IN PRACTIVE: THE LIFE CYCLE OF A MODELING PROJECT, FROM CONCEPTION TO PUBLICATION

- The example of Buruli ulcer in Cameroon -

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E^2M^2 Workshop

Ranomafana, November 2016

Steps in a modeling project

1. *Development of the study concept and question*
2. *Literature review*
3. *Data collection*
4. *Construction of model framework*
5. *Model analyses and selection*
6. *Model validation*
7. *Manuscript writing and submission*

Types of modeling studies

Without data collection

1. Purely theoretical studies
2. Parametrization based on published studies
   - Systematic reviews and meta-analyses
   - Experimental and field studies

1. Development of the study concept
2. Literature Review
3. Data collection
4. Construction of model framework
   - Dynamic equations and code
   - Relationships between parameters
5. Model analyses and selection
   - Parametrization
   - Simulations and debugging
6. Model validation
   - Model validation
   - Sensitivity analyses
7. Manuscript writing and submission

Types of modeling studies

1. Development of the study concept
2. Literature Review
3. **Data collection**
4. Construction of model framework
    - Statistical vs. Mathematical model
    - Model better adapted to our data
5. Model analyses and selection
    - Descriptive, univariate and multivariate
    - Parametrization and simulations
6. Model validation
    - Model validation, comparison
    - Sensitivity analyses
7. Manuscript writing and submission

With data collection

1. Data already collected for other purposes
    - Focus only on analyses
    - Need to understand data limitations and quality
    - Need to adapt modeling to the available data
2. Data collected for the modeling project
    - Very time consuming
    - Modeling is generally more straightforward

THE EXAMPLE OF BURULI ULCER IN CAMEROON

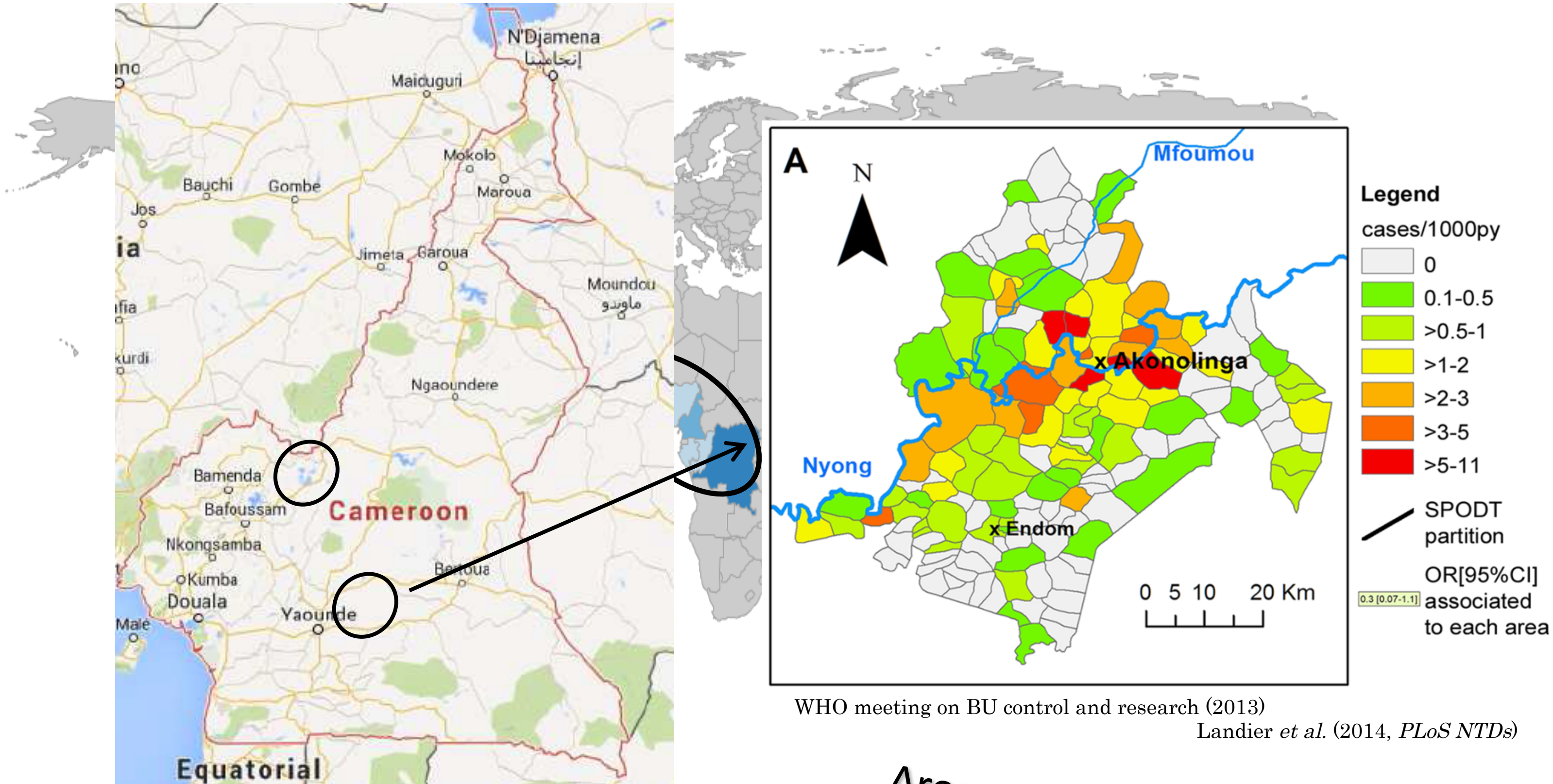
Buruli ulcer

Most affected : Children <15 years

25% cases with functional limitations

Source of images: www.who.int (2014)

Buruli ulcer: an emergent and neglected disease



WHO meeting on BU control and research (2013)

Landier *et al.* (2014, *PLoS NTDs*)

Around 5000 new cases each year

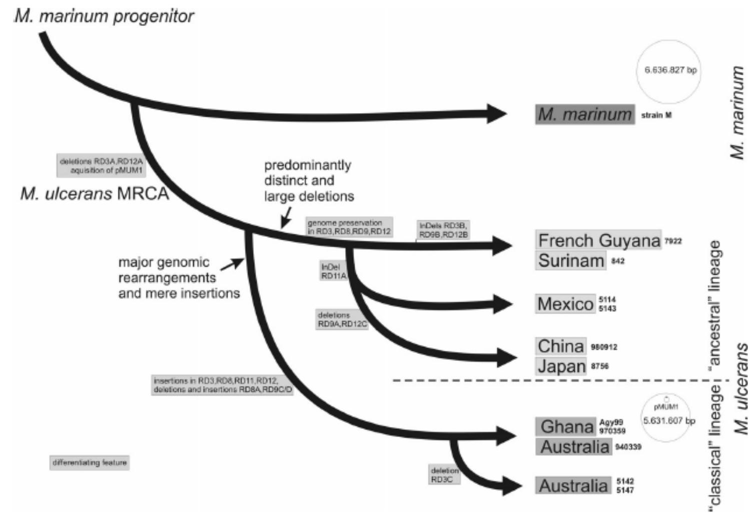
Cases in more than 30 countries

Focal distribution

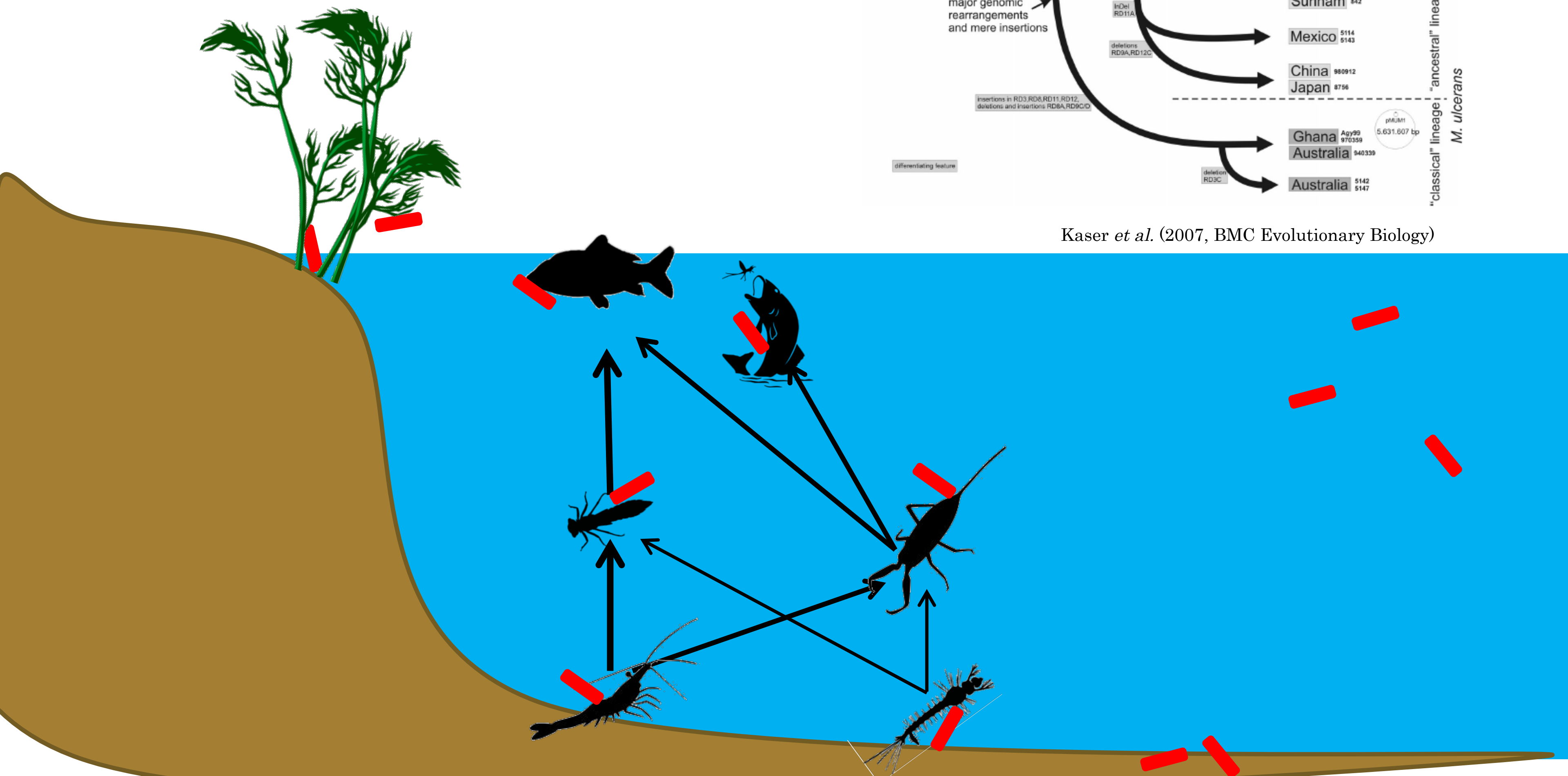
1. LITERATURE REVIEW
&
IDENTIFICATION OF THE PROBLEM

Mycobacterium ulcerans: generalities

Multi-host
&
Environmentally persistent



Kaser *et al.* (2007, BMC Evolutionary Biology)



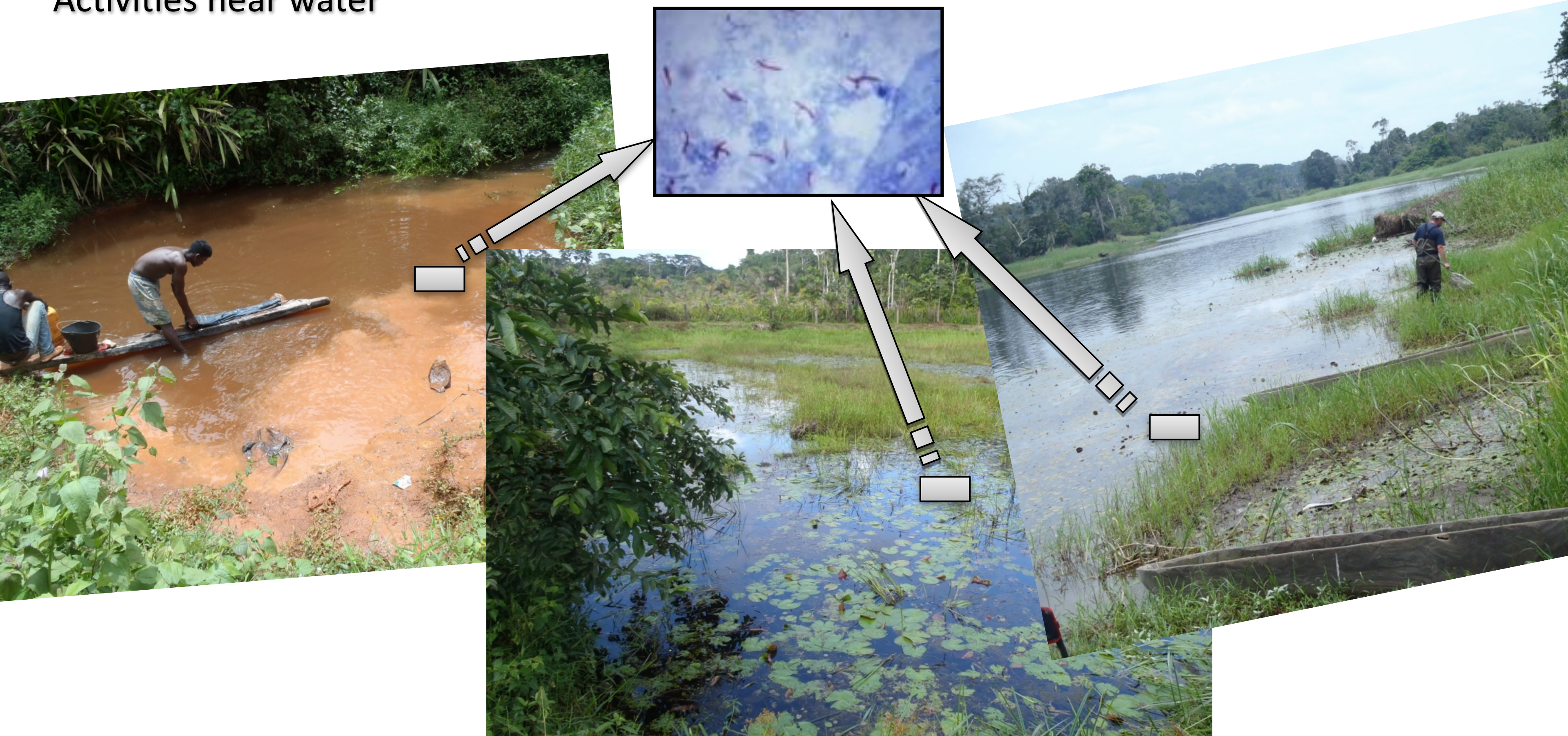
Buruli ulcer: a disease linked to aquatic ecosystems

BU Risk factors

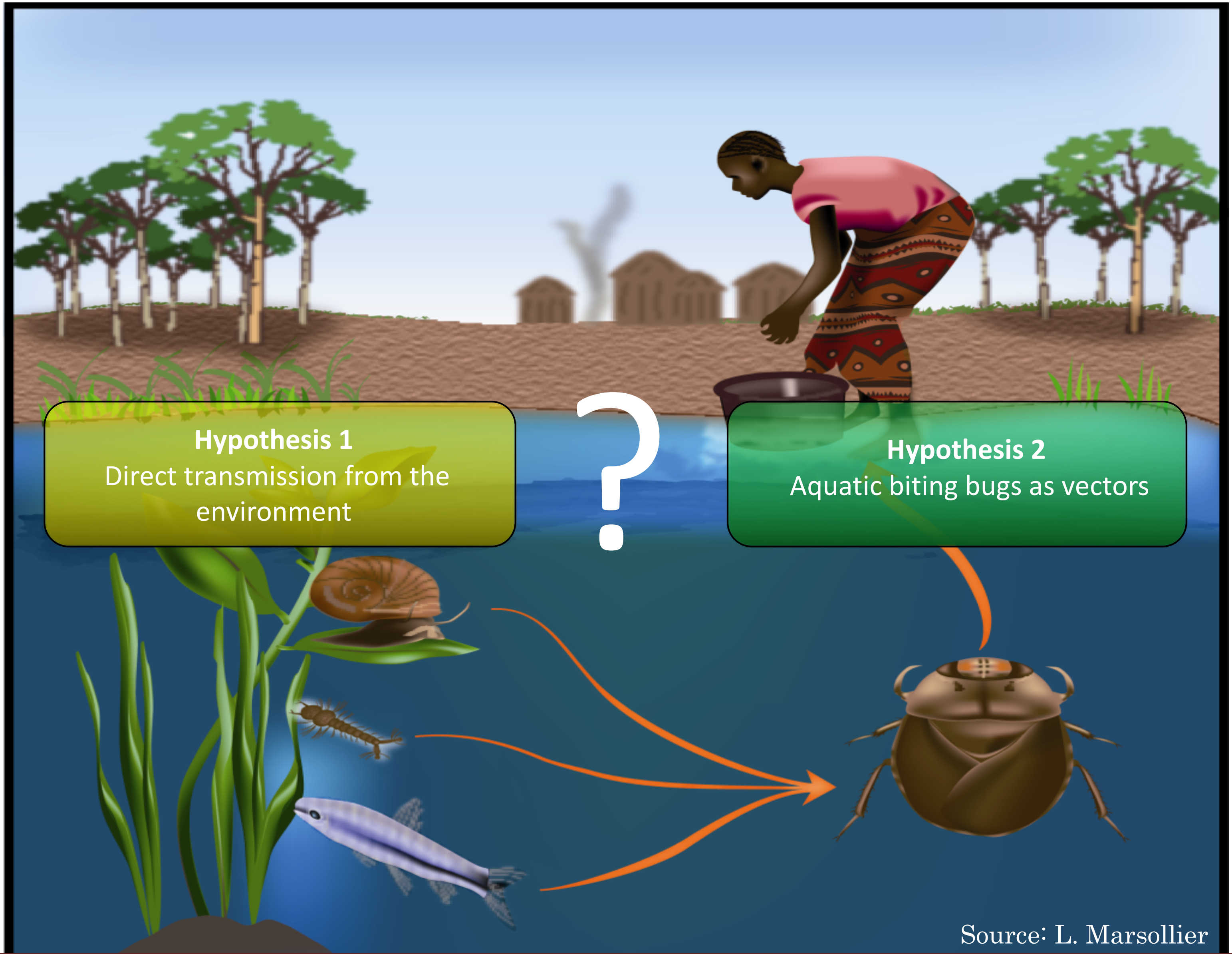
Proximity to stagnant or slow flowing waters

Activities near water

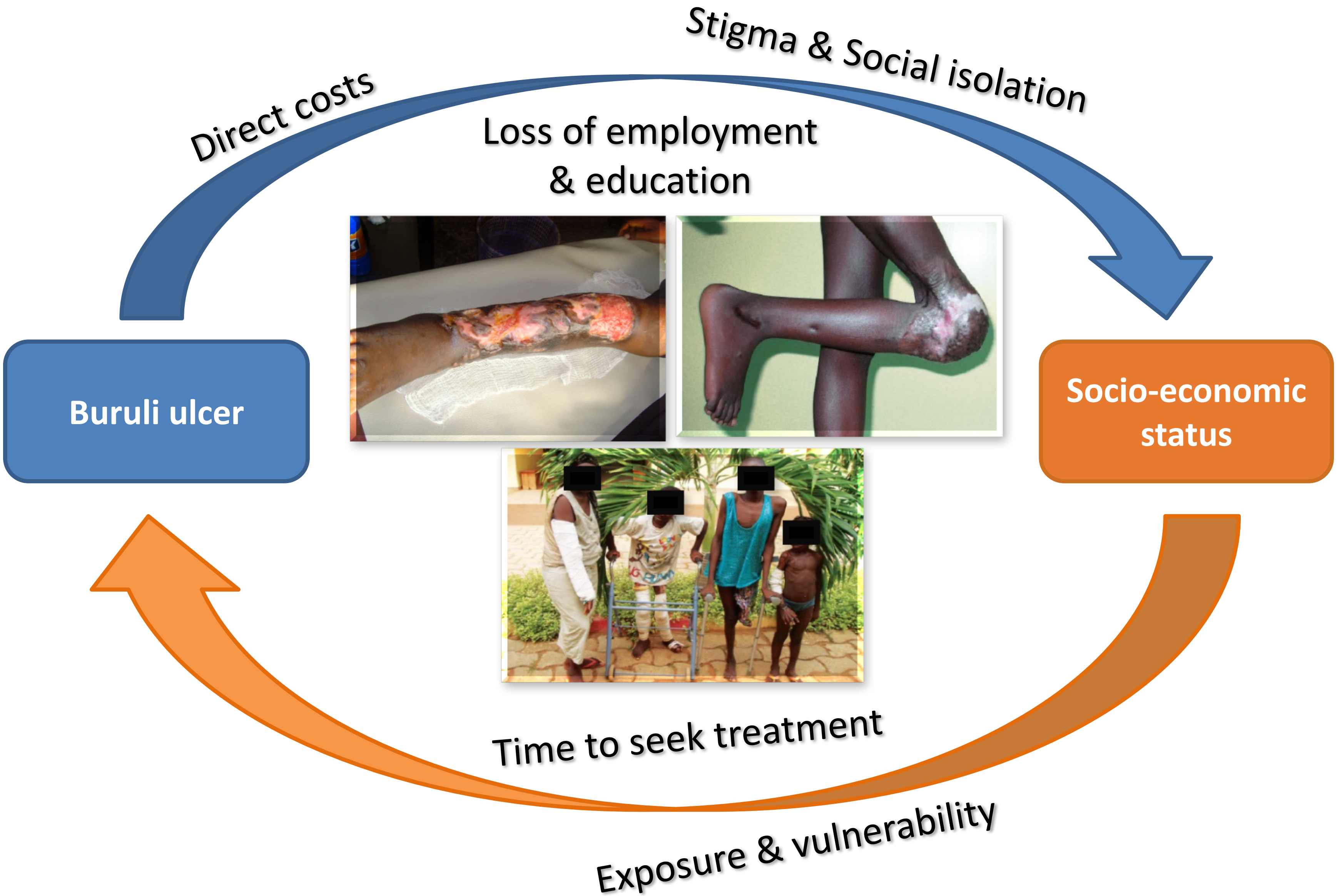
M. ulcerans



Buruli ulcer: a mysterious disease



ii Buruli ulcer: socio-economic feedbacks

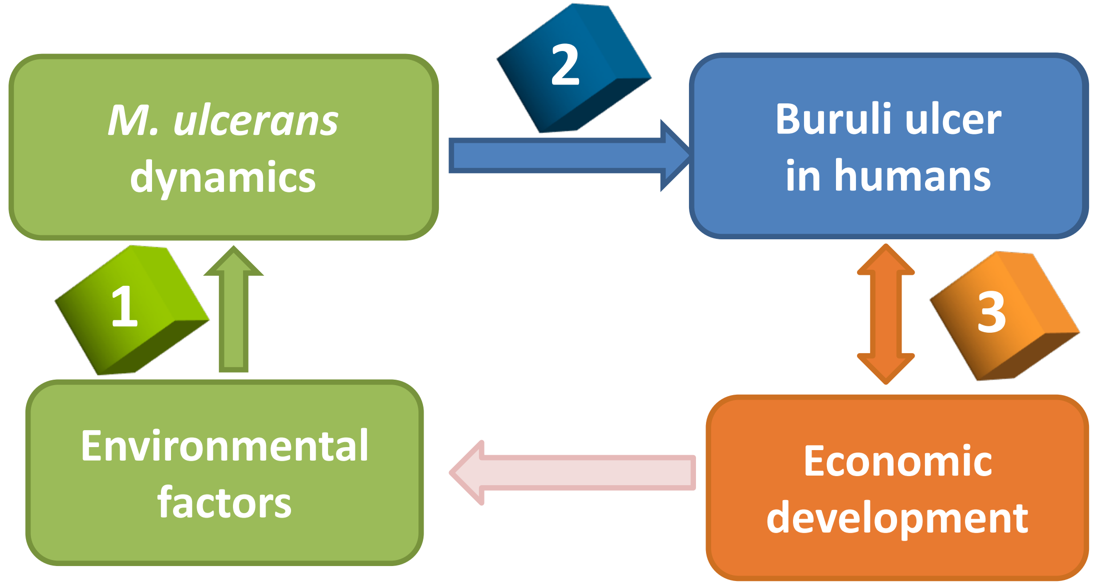


2. STUDY DESIGN & OBJECTIVES

iii Objectives of the project

General objective

To gain insight on the links between ecological factors, human diseases and economic development, **through the case study of Buruli ulcer disease**.



Specific objectives

1. To understand the effects of environmental factors on *M.ulcerans* ecology
2. To study the transmission of *M.ulcerans* from the aquatic environment to humans
3. To understand the feedbacks between poverty and Buruli ulcer

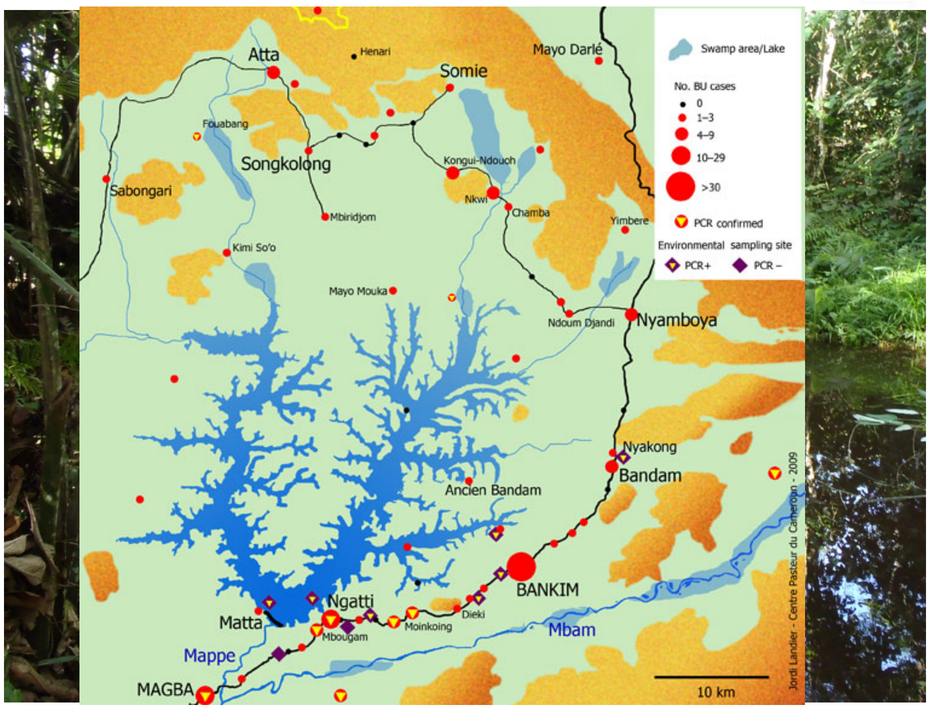
Regions of study

Akonolinga

- Landscape: Tropical rainforest
- Historically endemic area (>40 years)

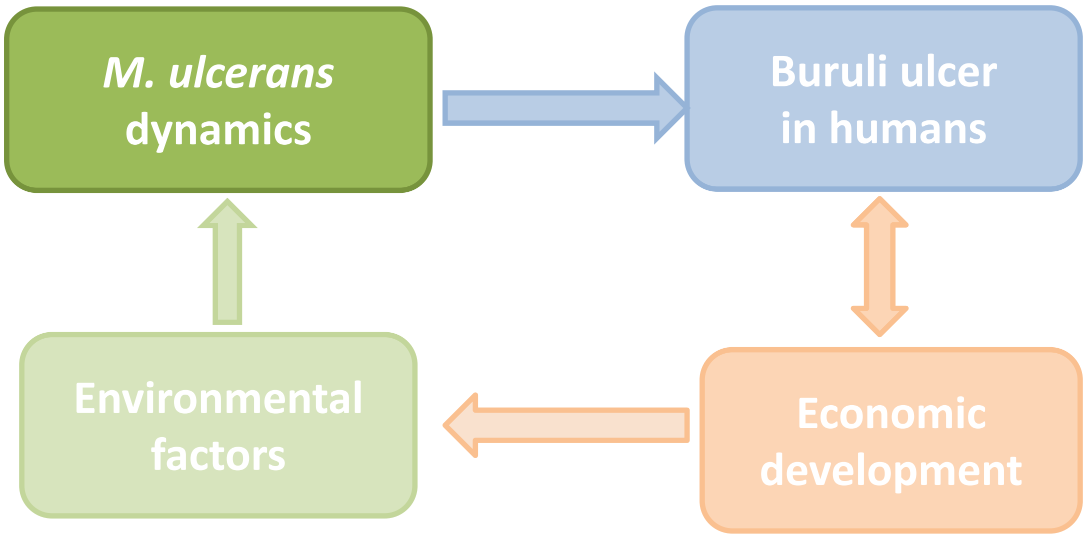
Bankim

- Landscape: Savannah-Forest
- New endemic area (10 years)



Marion *et al.* (2011, *EID*)

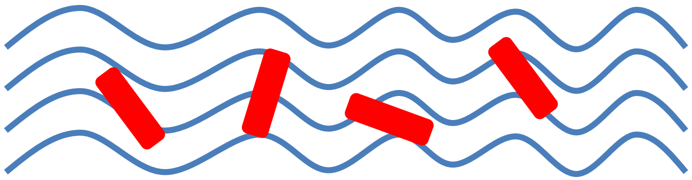
Landier *et al.* (2014, *PLoS NTDs*)

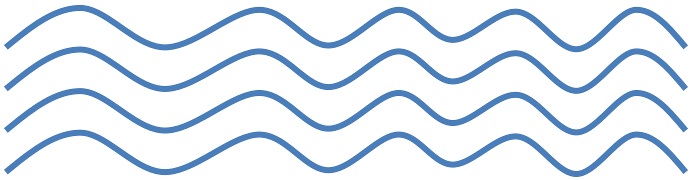


3. DATA COLLECTION & DESCRIPTIVE ANALYSES

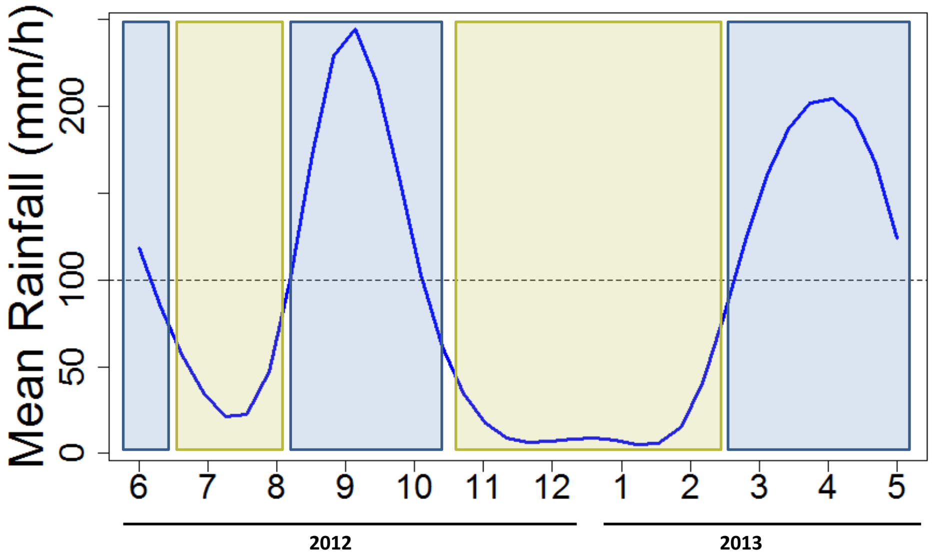

Favourable environments


Unfavourable environments





1 Introduction



Characterization of MU in the environment

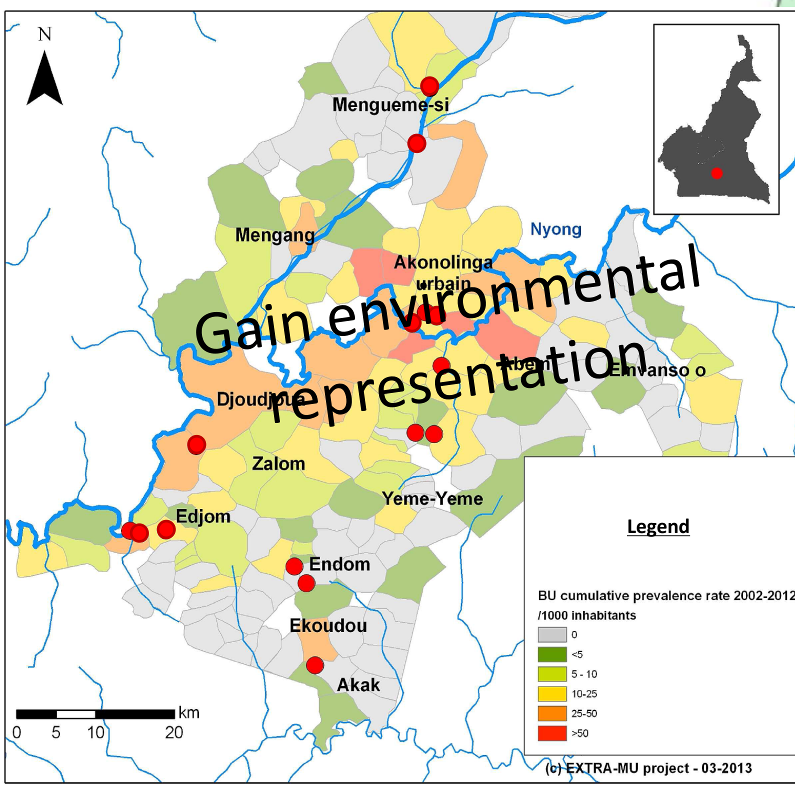
1 Sample sites: Regions

Akonolinga

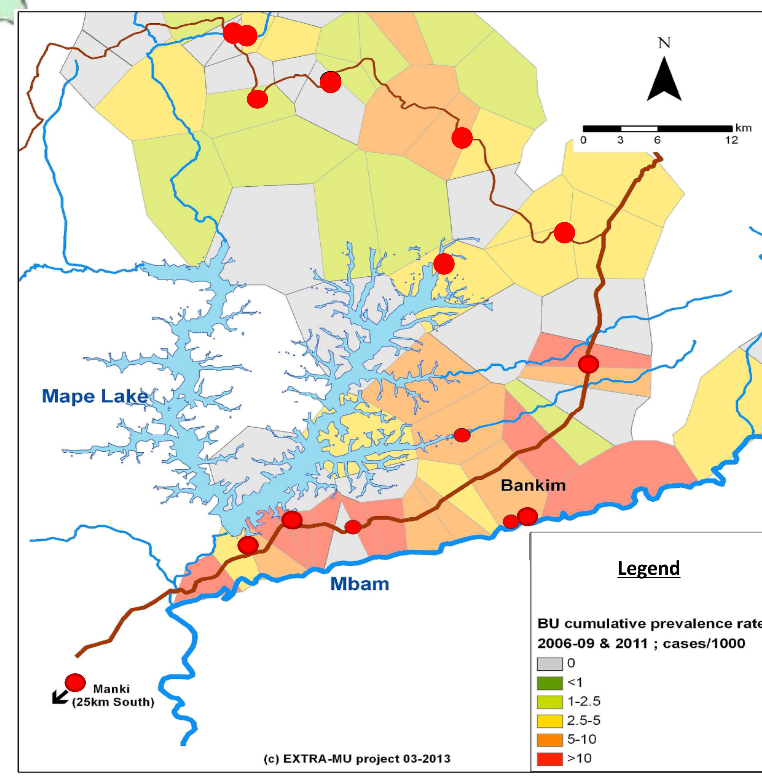
- 16 water bodies
- Samples once every month (x12)

Bankim

- 16 water bodies
- Samples once every three months (x4)



Gain environmental representation



1 Ecology of M.ulcerans: Sample sites

Rivers

Swamps

Streams

Flooded areas

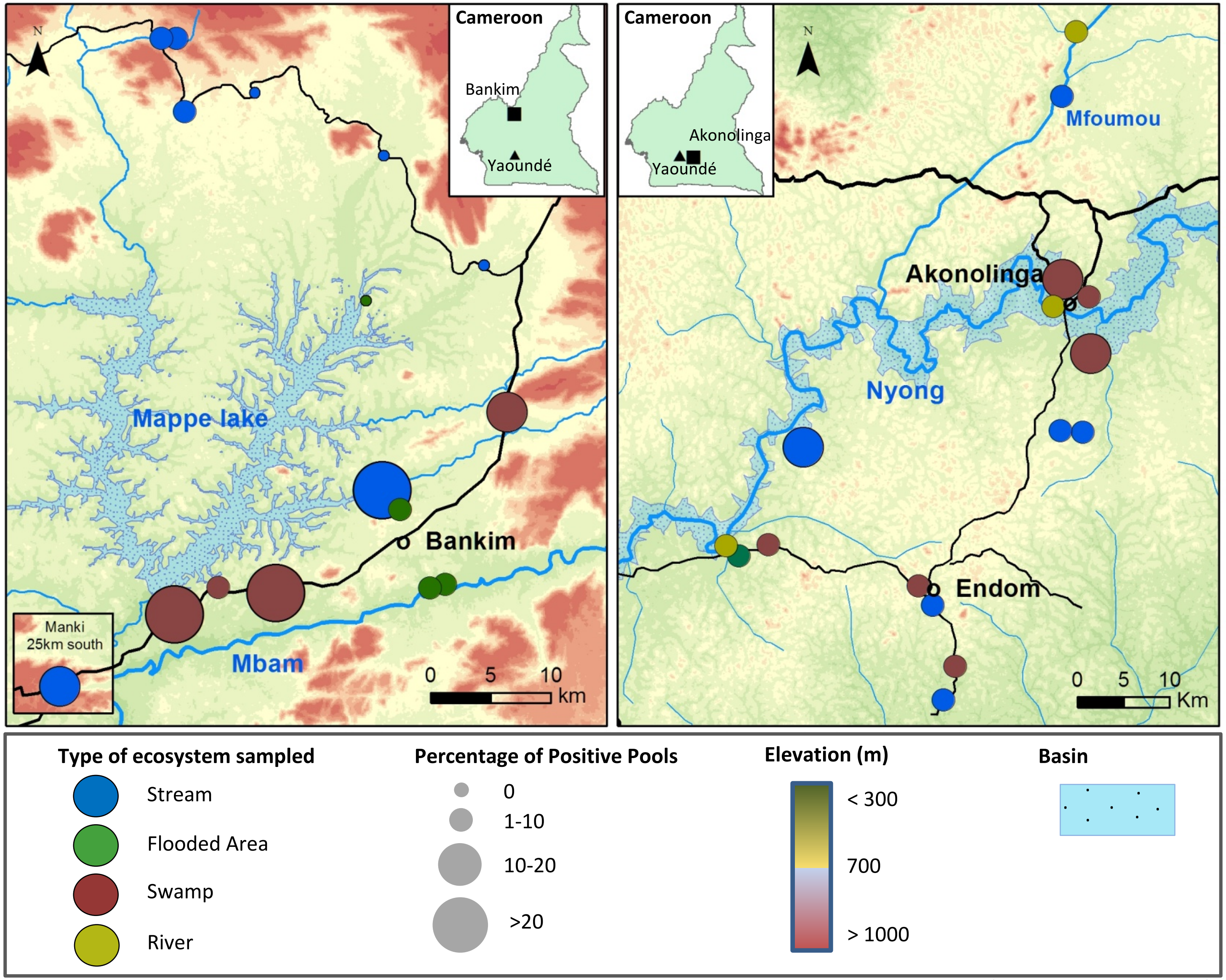
1. Fieldwork: Environmental sampling

2. Laboratory (CPC): Taxonomic identification & Pool composition

3. Laboratory (Angers): DNA extraction & Amplification

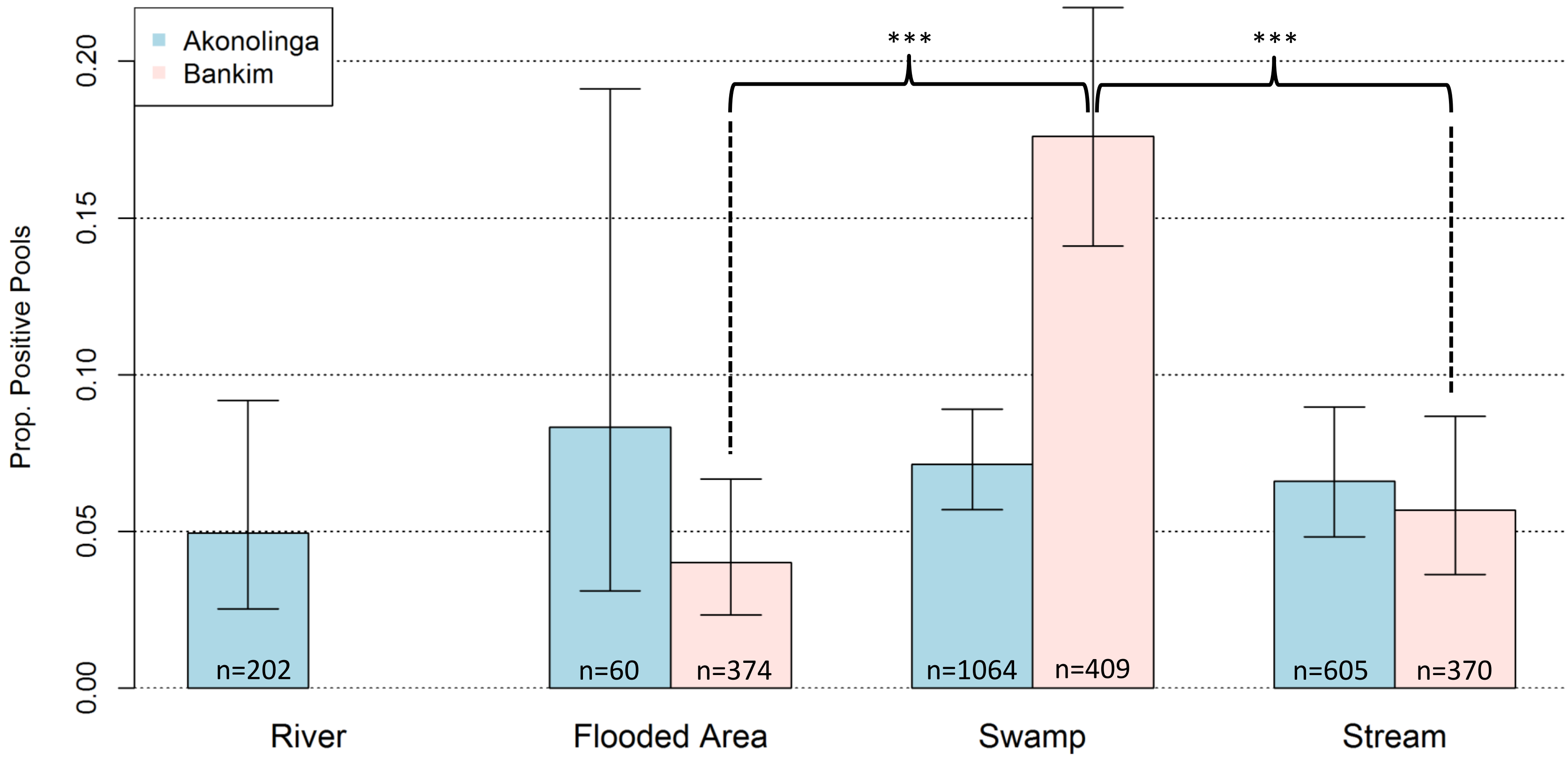
Characterization of MU in the environment

M. ulcerans geographical distribution



Garchitorena *et al.* (2014, *PloS NTDs*)

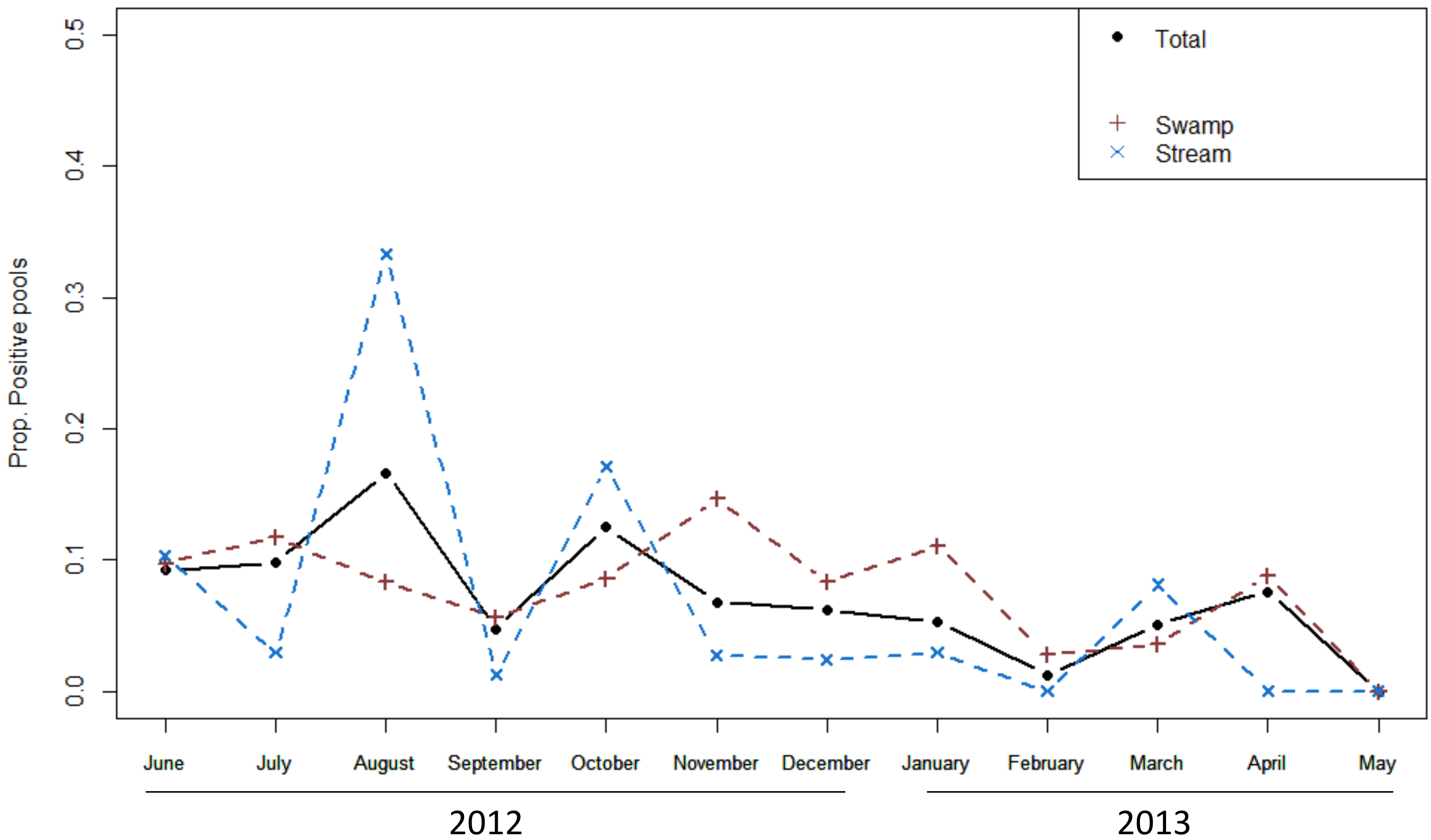
1 *M. ulcerans* distribution in freshwater ecosystems



*** $p < 0.001$; Chi^2 Test

Garchitorena *et al.* (2014, *PloS NTDs*)

1 Seasonal fluctuations of *M. ulcerans in* freshwater ecosystems



Garchitorena *et al.* (2014, *PloS NTDs*)

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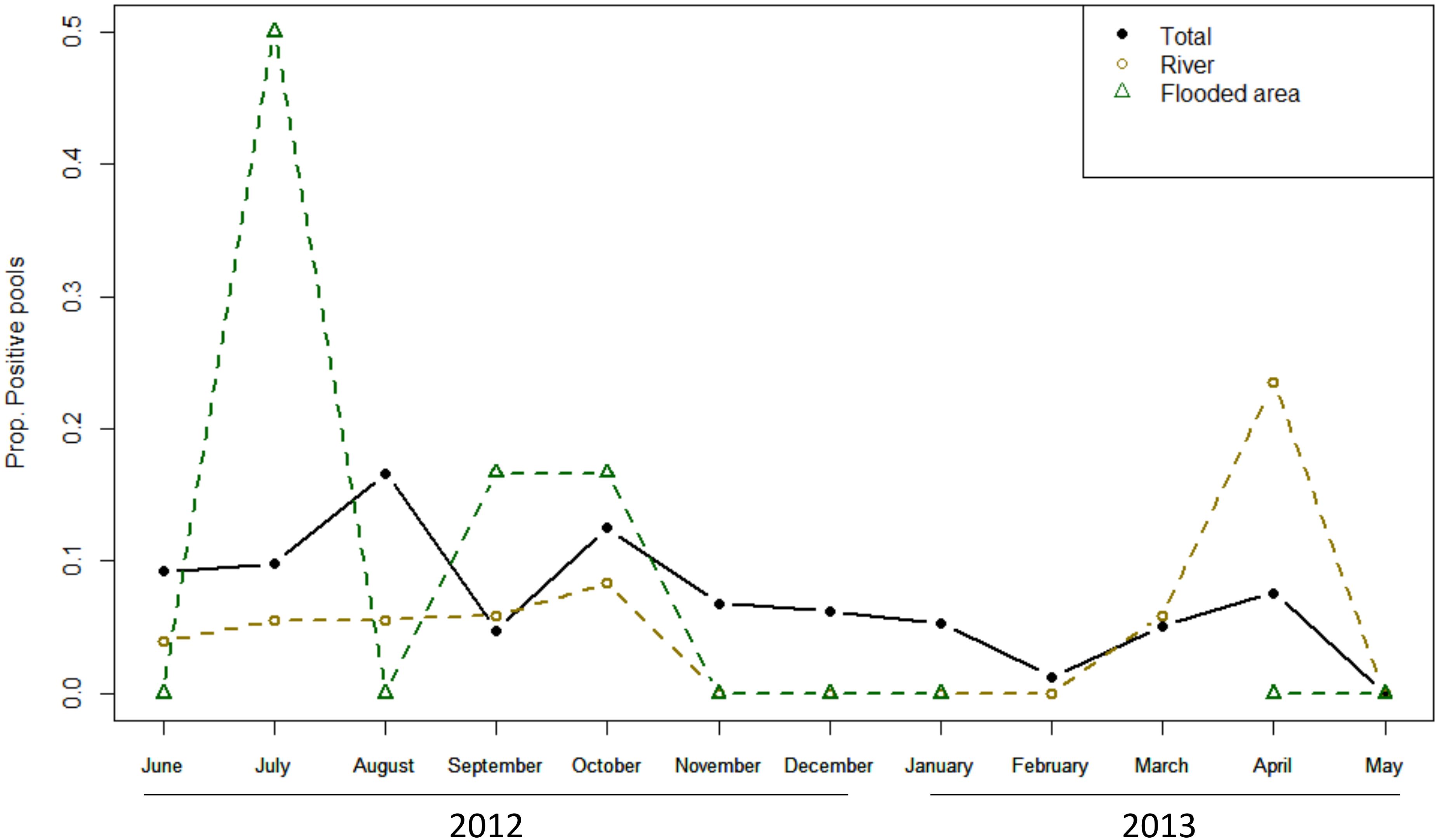
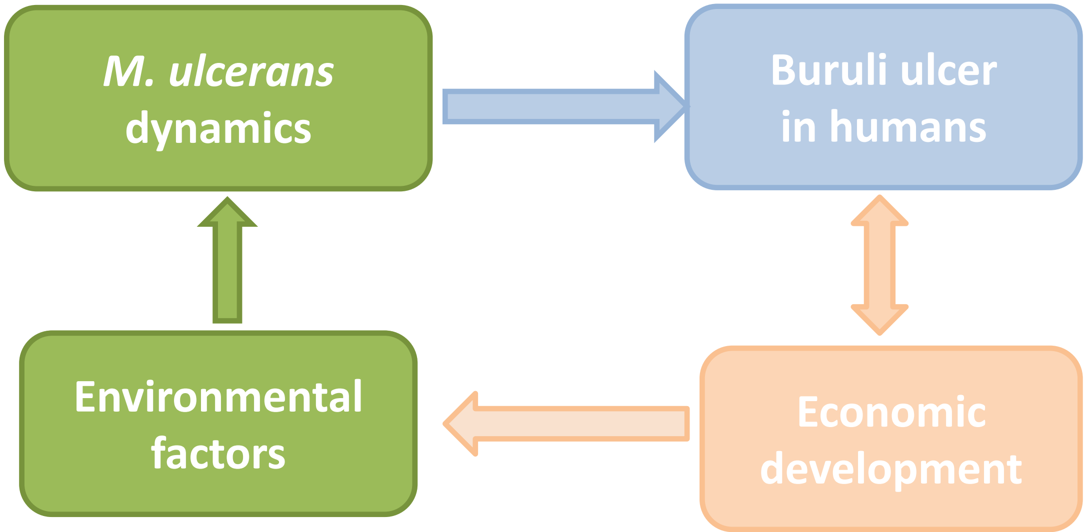
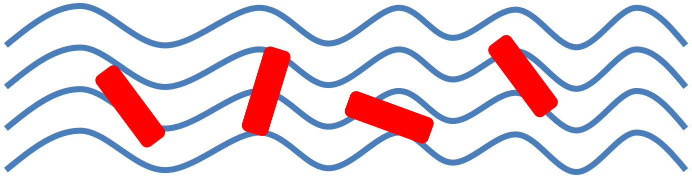


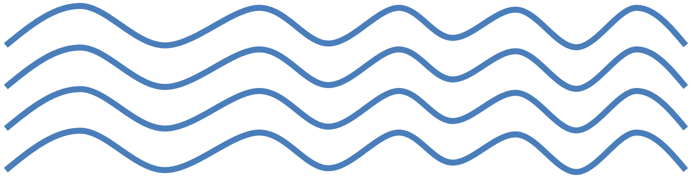
Garchitorena *et al.* (2014, *PloS NTDs*)



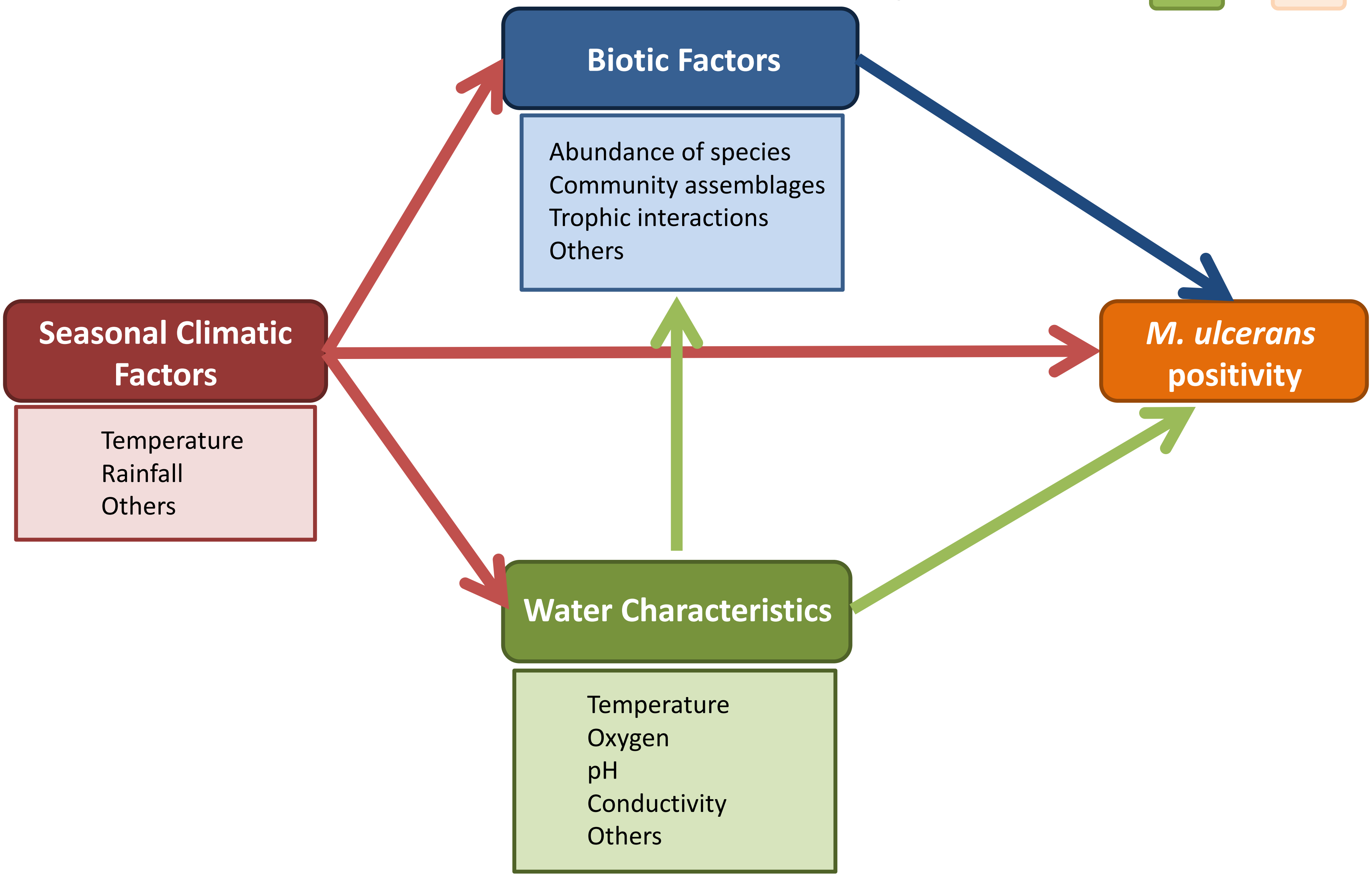
4. STATISTICAL ANALYSES TO UNDERSTAND M. ULCERANS ECOLOGY

1 Introduction





2 Environmental drivers of *M. ulcerans*



2 Methodology: Multi-model approach

Model Definition

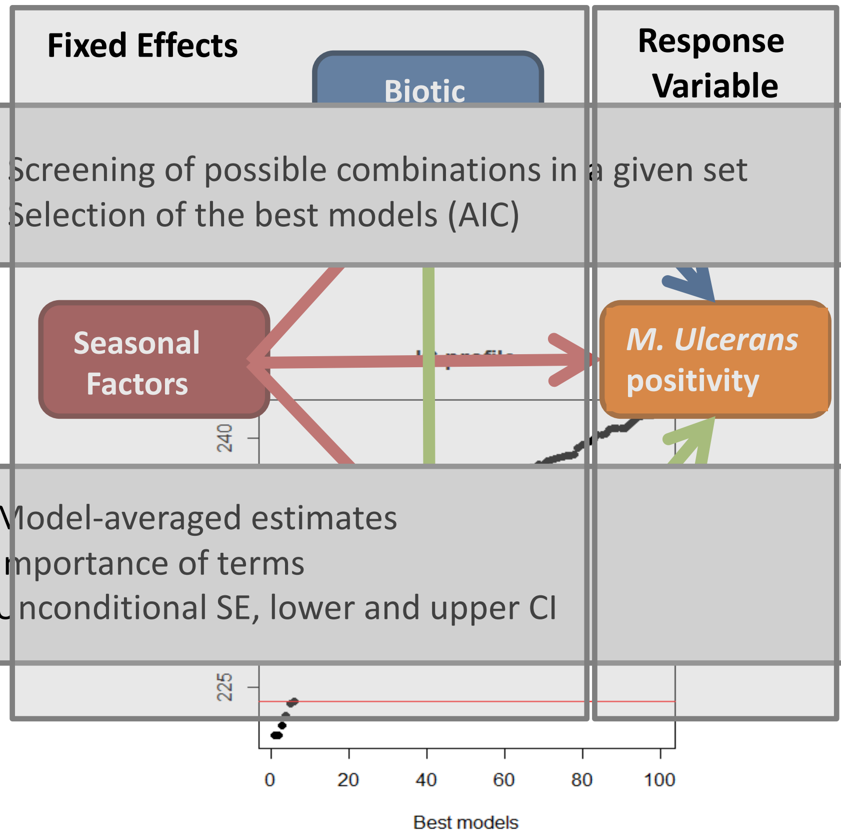
- Generalized linear mixed models
- **Random effect**: Sample site

Multi-model Selection

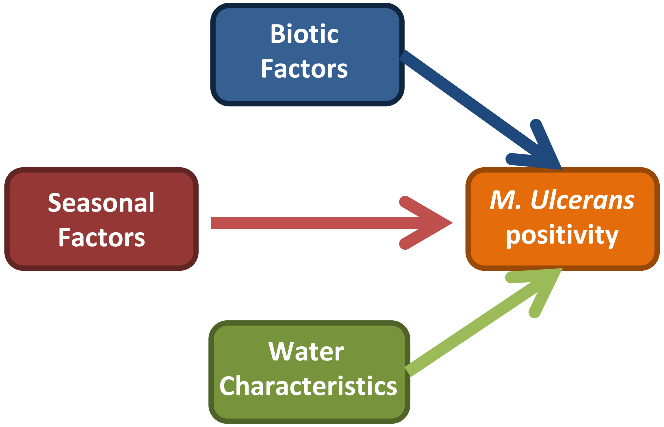
- Screening of possible combinations in a given set
- Selection of the best models (AIC)

Multi-model Inference

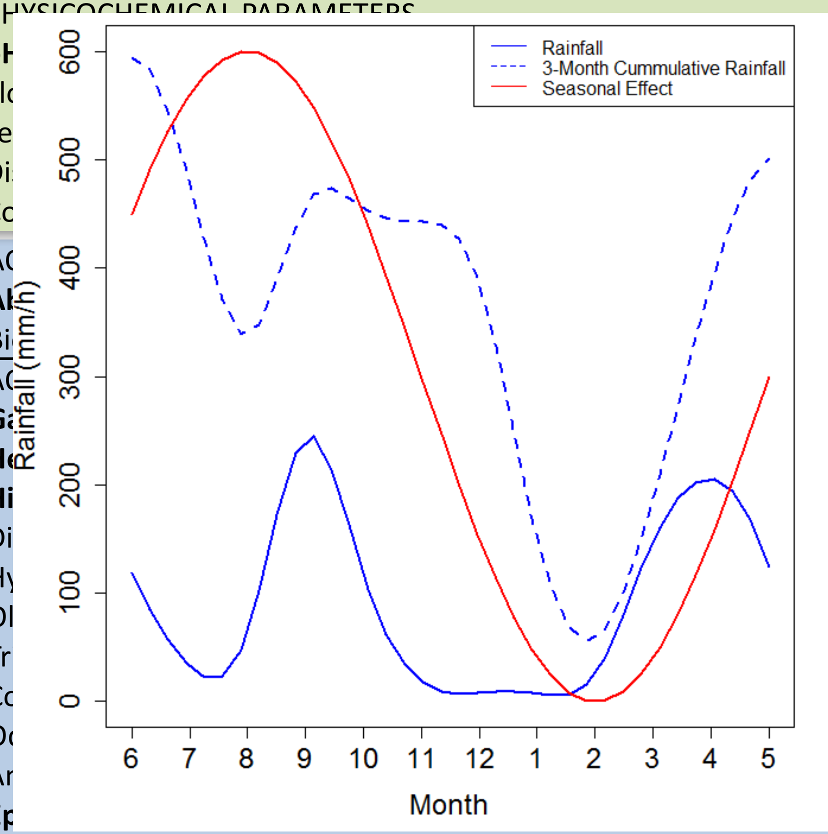
- Model-averaged estimates
- Importance of terms
- Unconditional SE, lower and upper CI



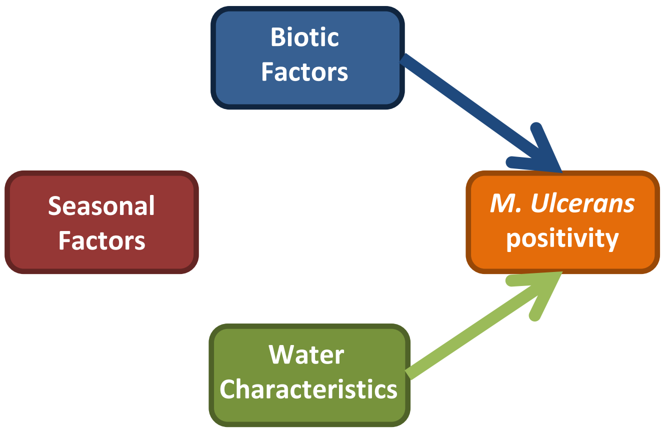
2 Environmental drivers of *M. ulcerans:* Akonolinga



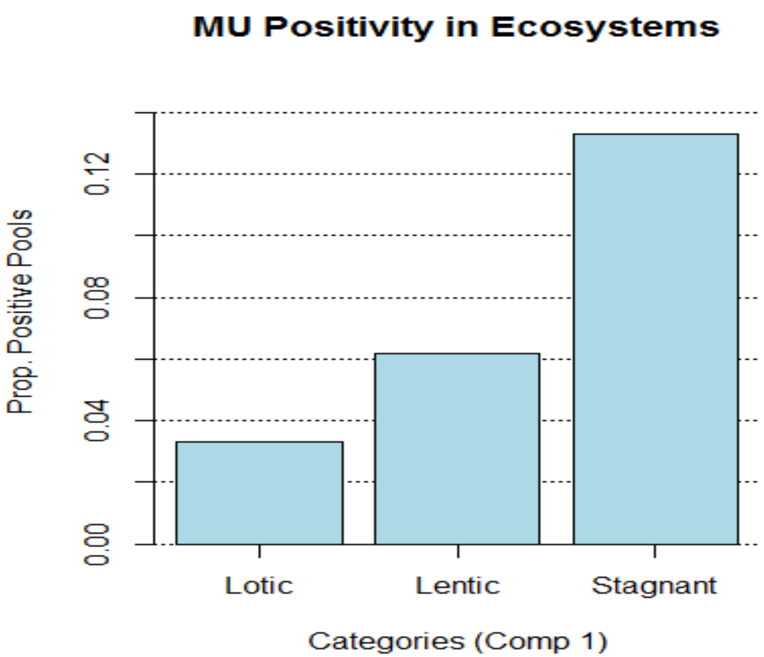
Variable	Avg.beta	Lower.CL	Upper.CL	Relative Importance
(Intercept)	**-13,66**	**-22,50**	**-4,82**	**1**
SEASONALITY				
Sin(2pi*Mois/12)	**0,35**	**0,02**	**0,69**	**1**
Sin(2pi*Mois/4)				
Cos(2pi*Mois/12)				
Cos(2pi*Mois/4)				
PHYSICOCHEMICAL PARAMETERS				
pH				
Flo				
Te				
Di				
Co				
AC				
Al				
Bi				
AC				
Ga				
He				
Hi				
Di				
Hy				
Ol				
Tr				
Co				
Od				
Ar				
Ep				
Decapoda	**-1,01**	**-1,81**	**-0,21**	**0,21**

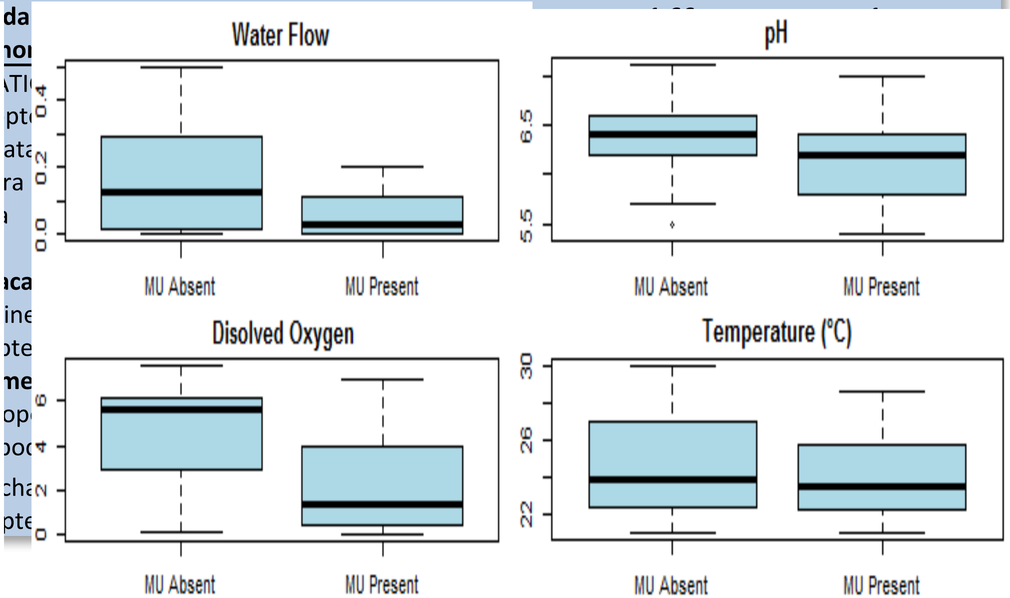


2 Environmental drivers of *M. ulcerans:* Bankim

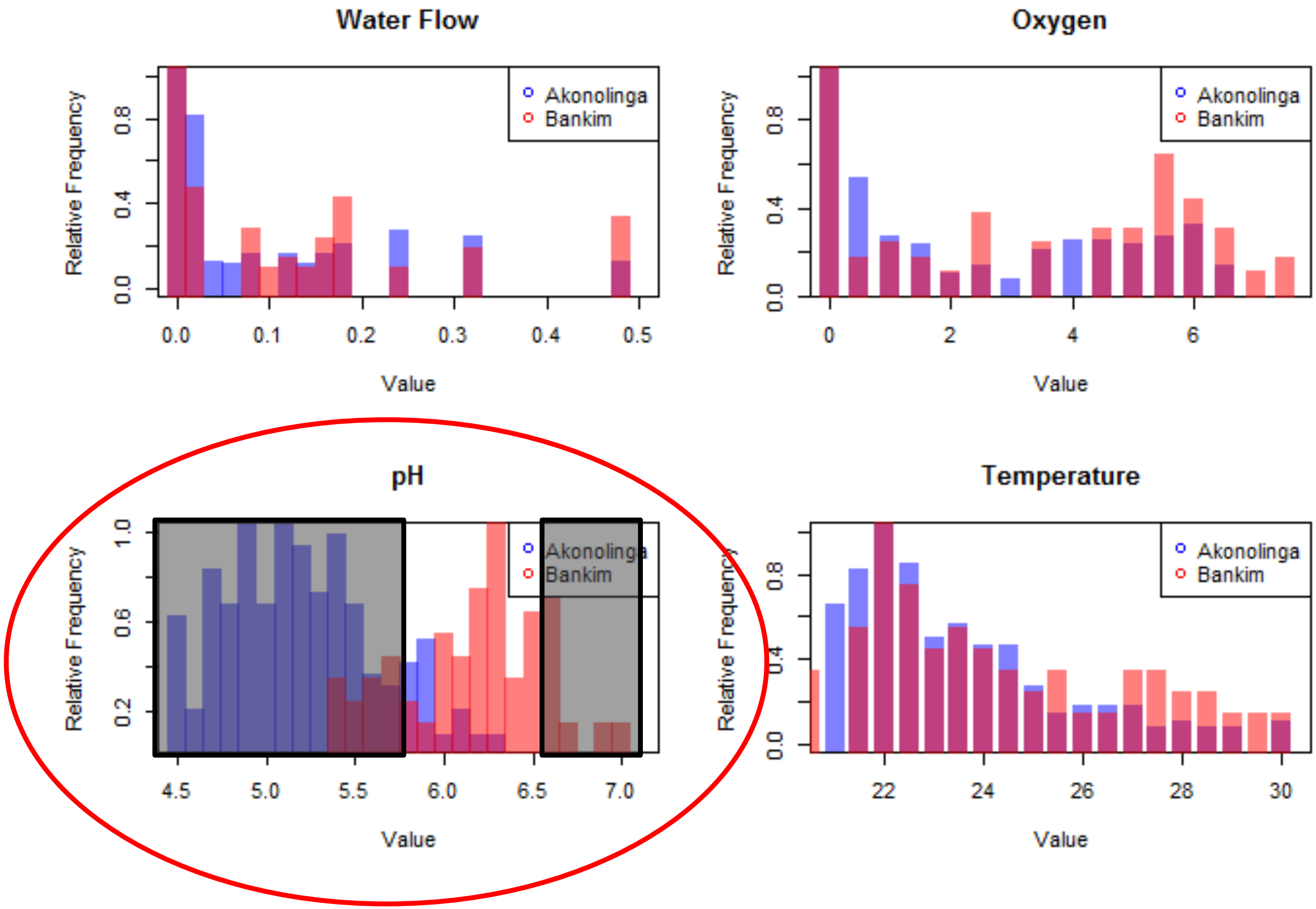


Variable	Avg.beta	Lower.CL	Upper.CL	Relative.Importance
(Intercept)	**-10,13**	**-18,94**	**-1,32**	**1**
PHYSICO-CHEMICAL PARAMETERS				
Water Flow (lentic)	**-1,91**	**-3,25**	**-0,57**	**1**
Water Flow (lotic)	**-2,86**	**-4,38**	**-1,33**	**1**
pH	-5,52	-15,64	4,61	0,02
Temperature				
Dissolved Oxygen				
Conductivity				
Comp3	0,24	-0,57	1,06	0,05
Comp1	0,34	-0,24	0,92	0,02
Comp2	-0,16	-0,85	0,53	0,01
COMMUNITY				





2 Why the two regions are so different?

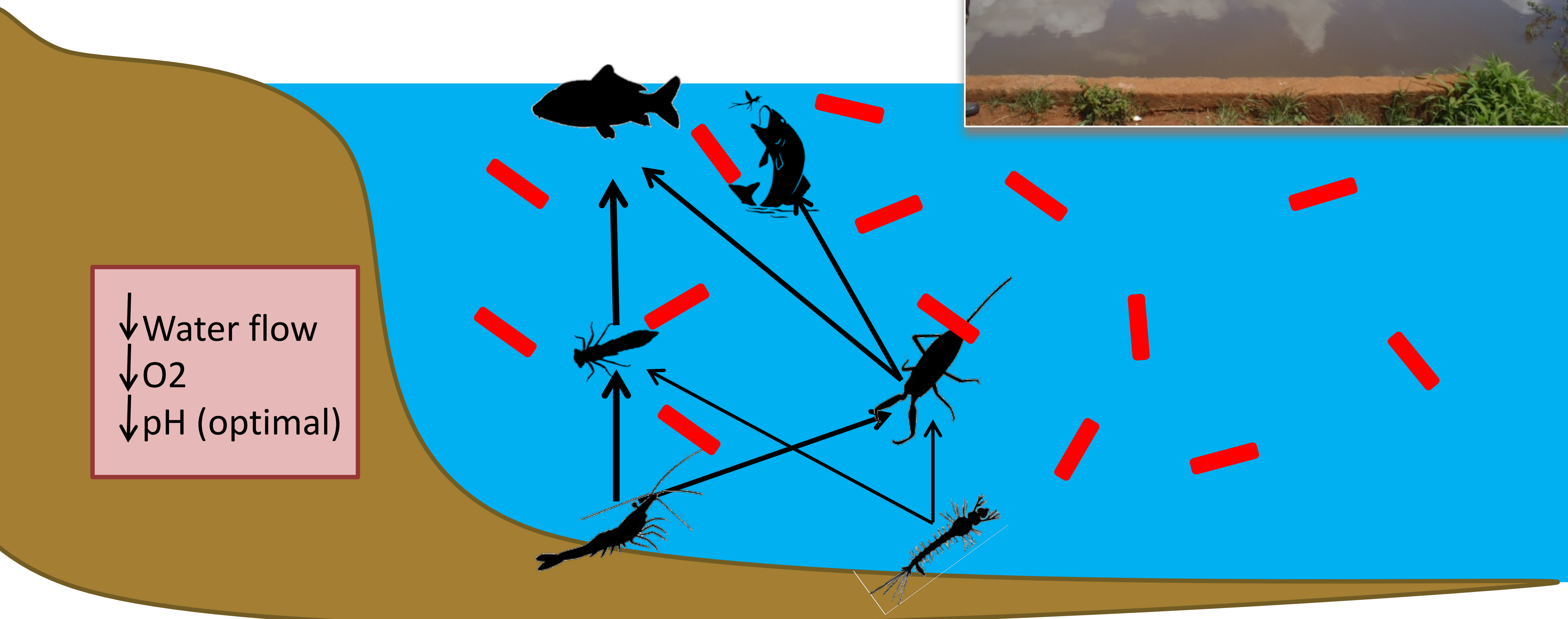


Optimal *pH* for *MU* [5.8-6.5]

2 Our theory

Scenario 1: Favourable physico-chemical conditions

Free living stages
&
Environmental transmission to aquatic organisms

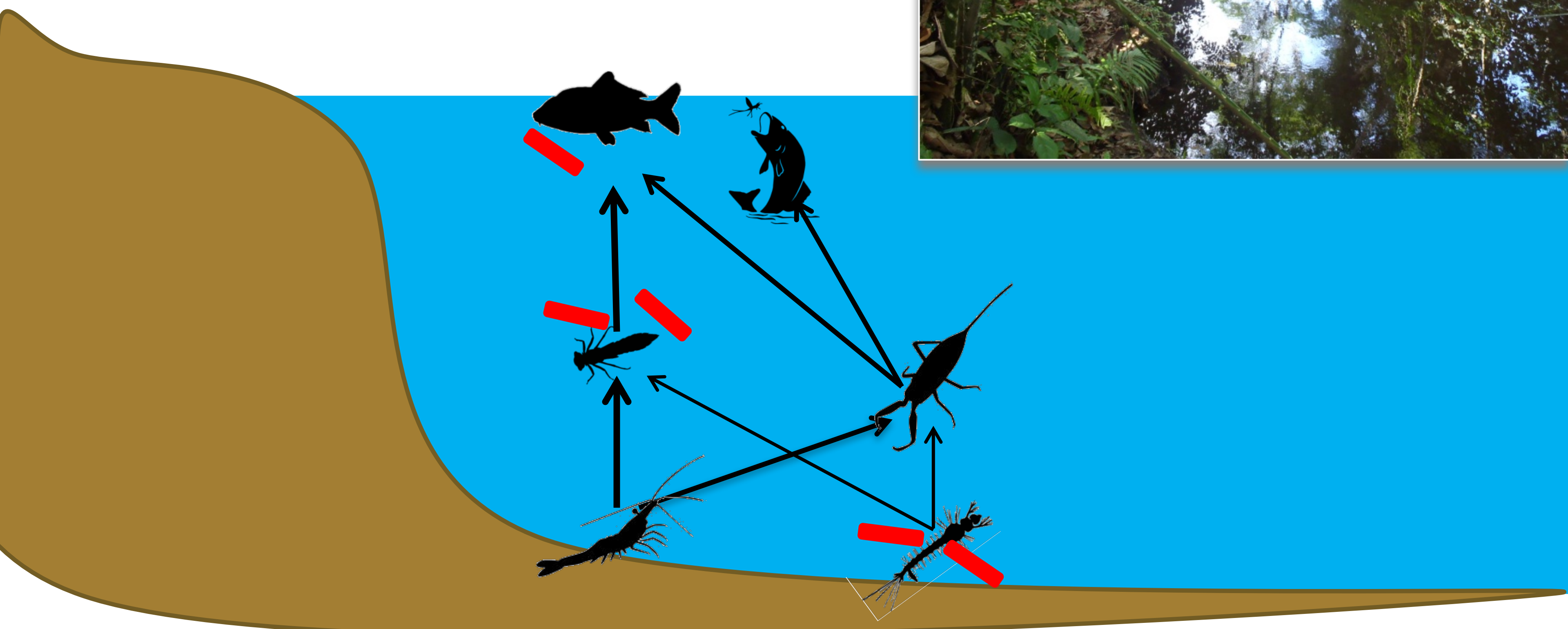


Environmental drivers of MU

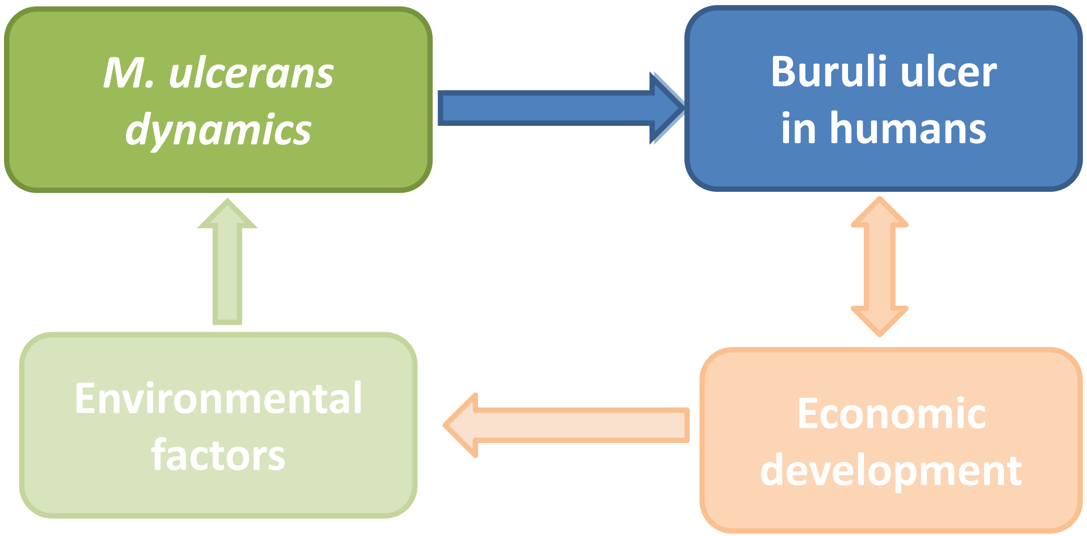
2 Our theory

Scenario 2: Adverse physico-chemical conditions

Mostly intra-host
&
Trophic transmission

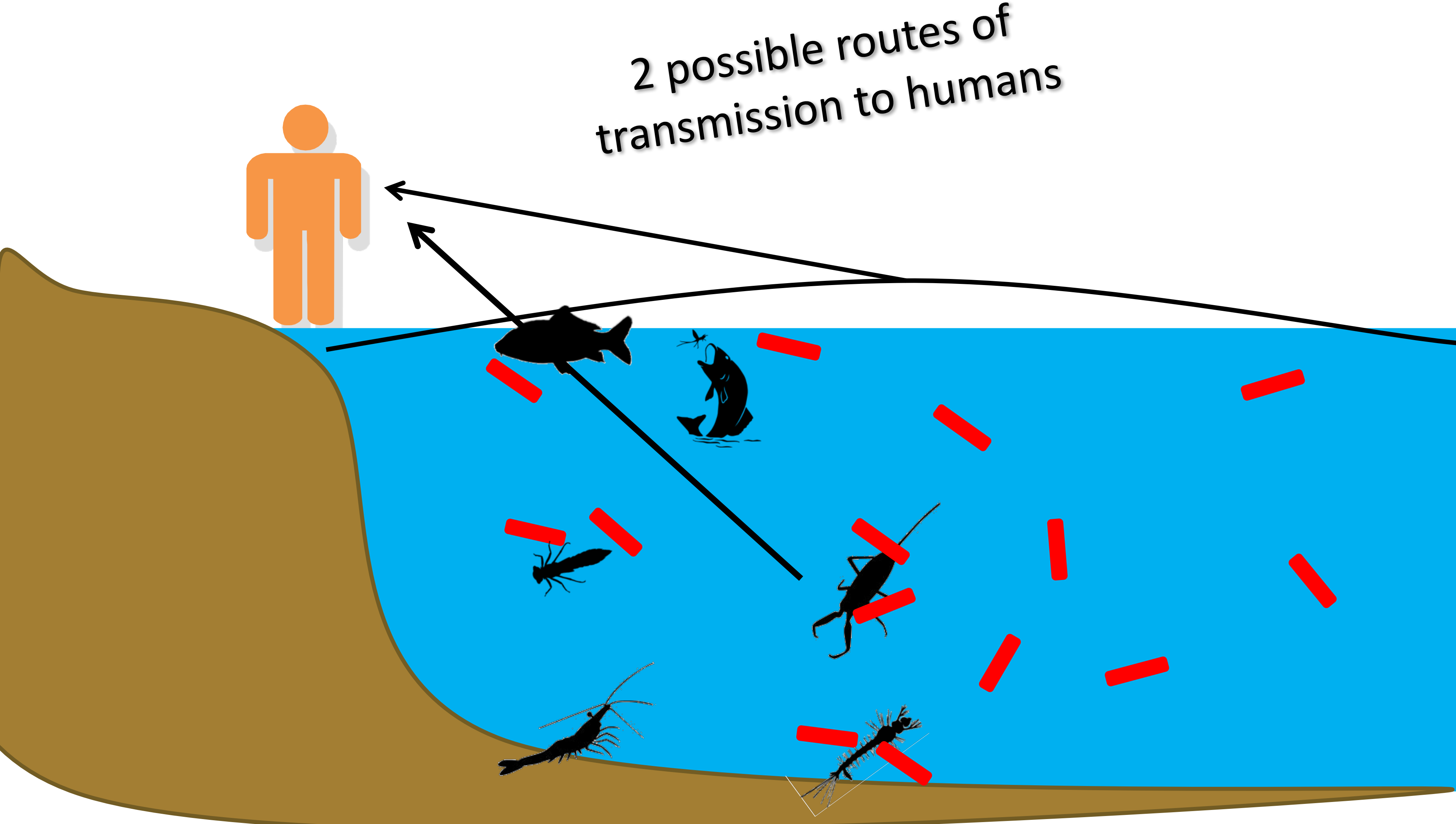


Environmental drivers of MU



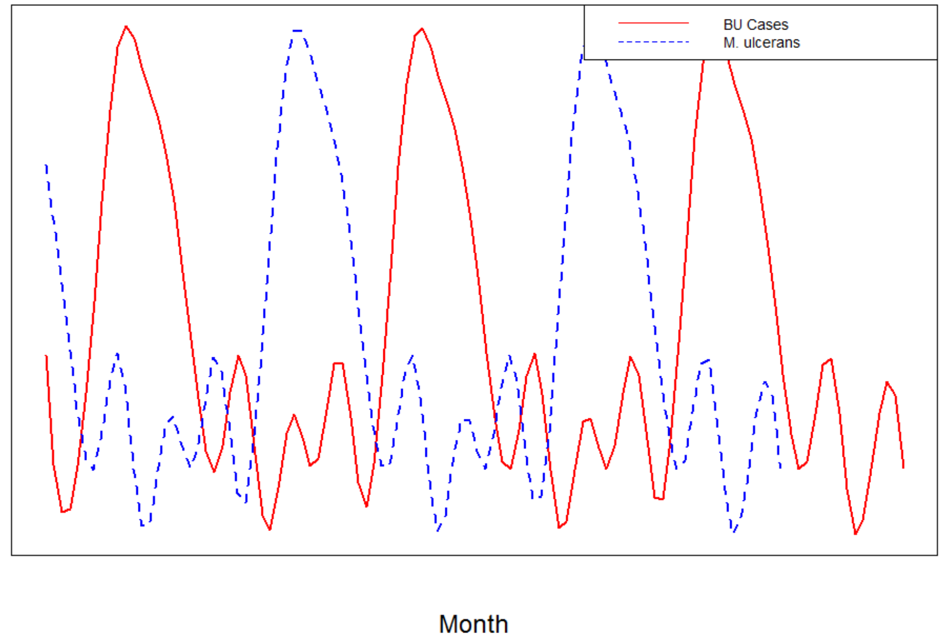
5. MATHEMATICAL MODELING TO UNDERSTAND BU TRANSMISSION

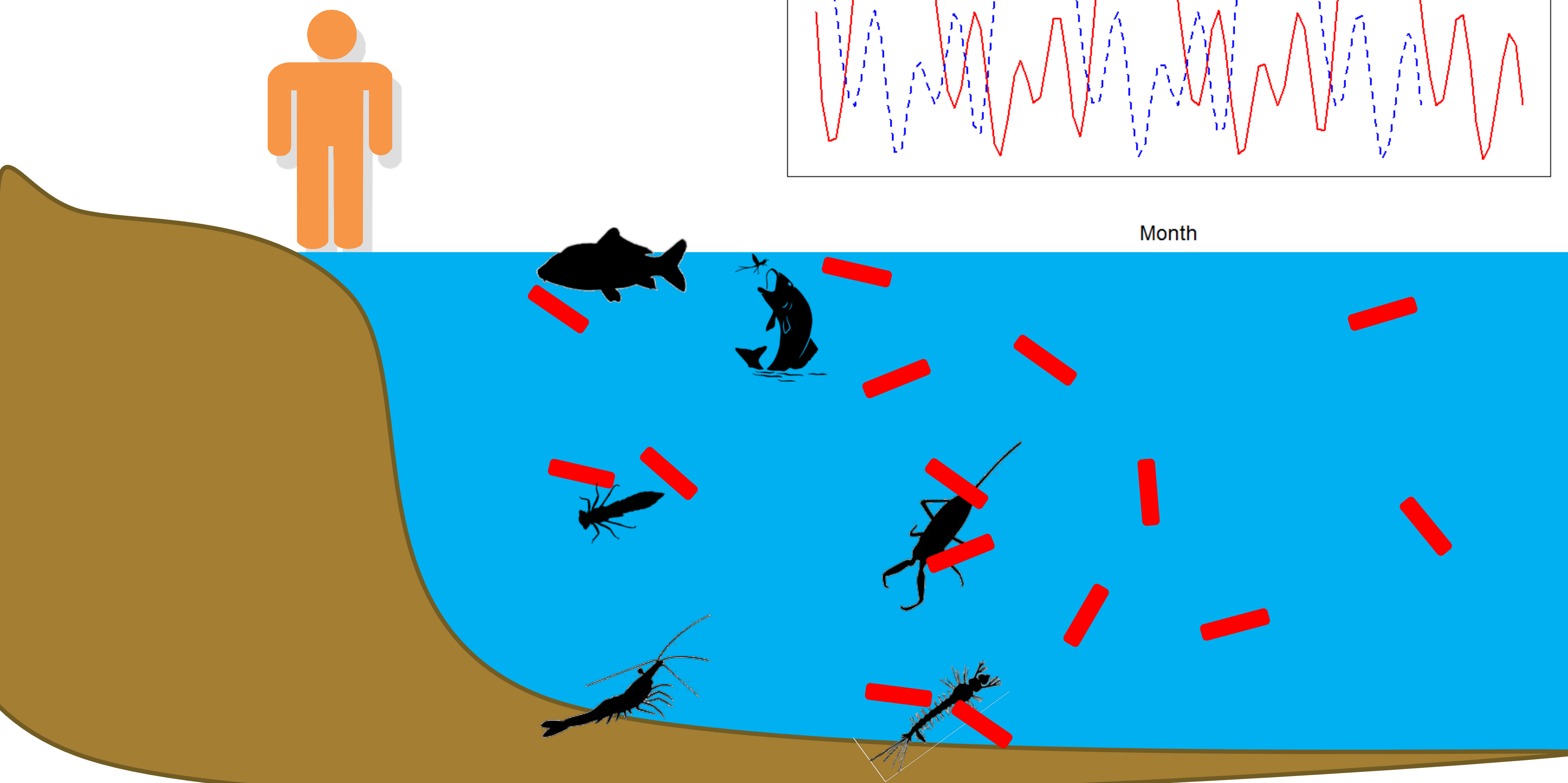
Introduction



3 Introduction

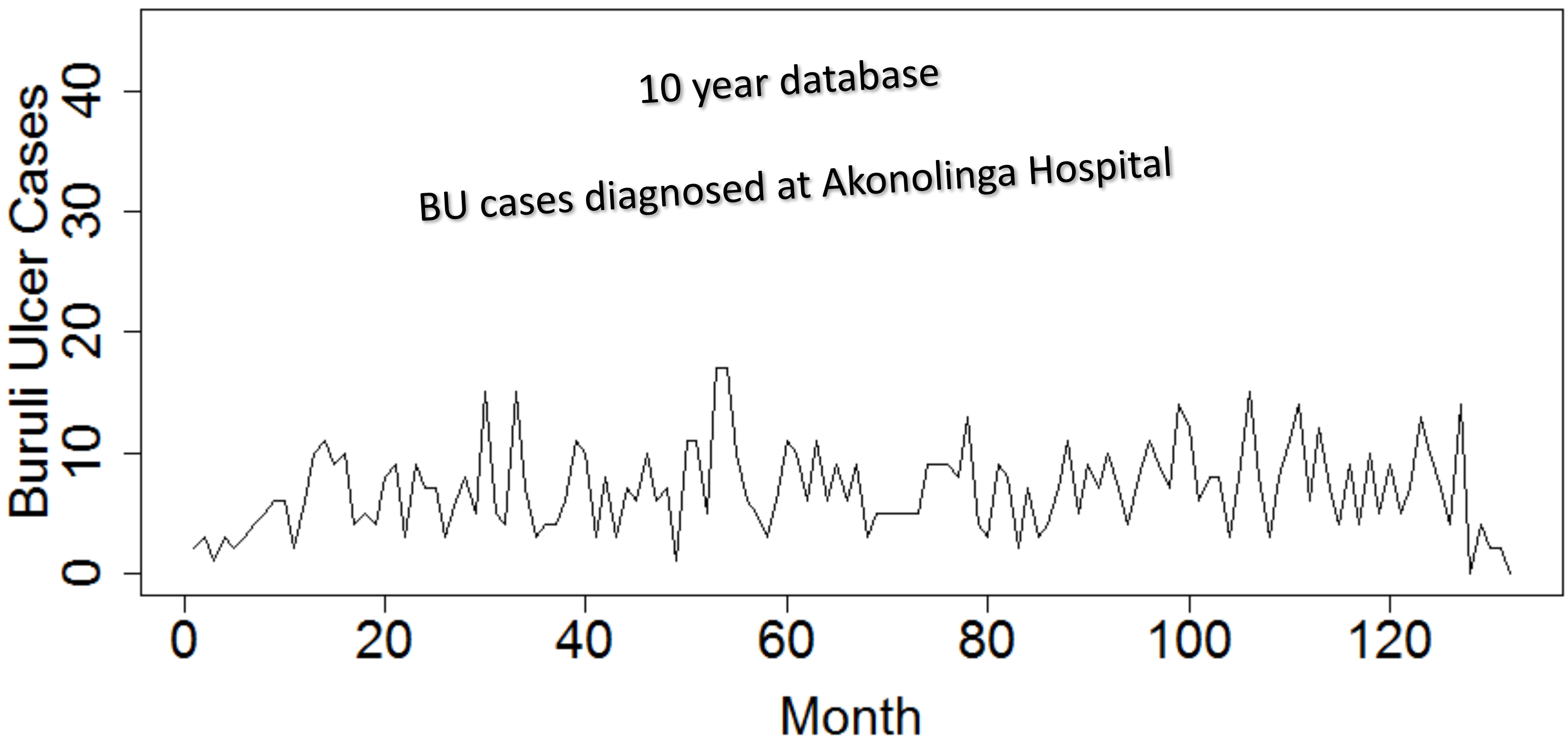
Temporal model





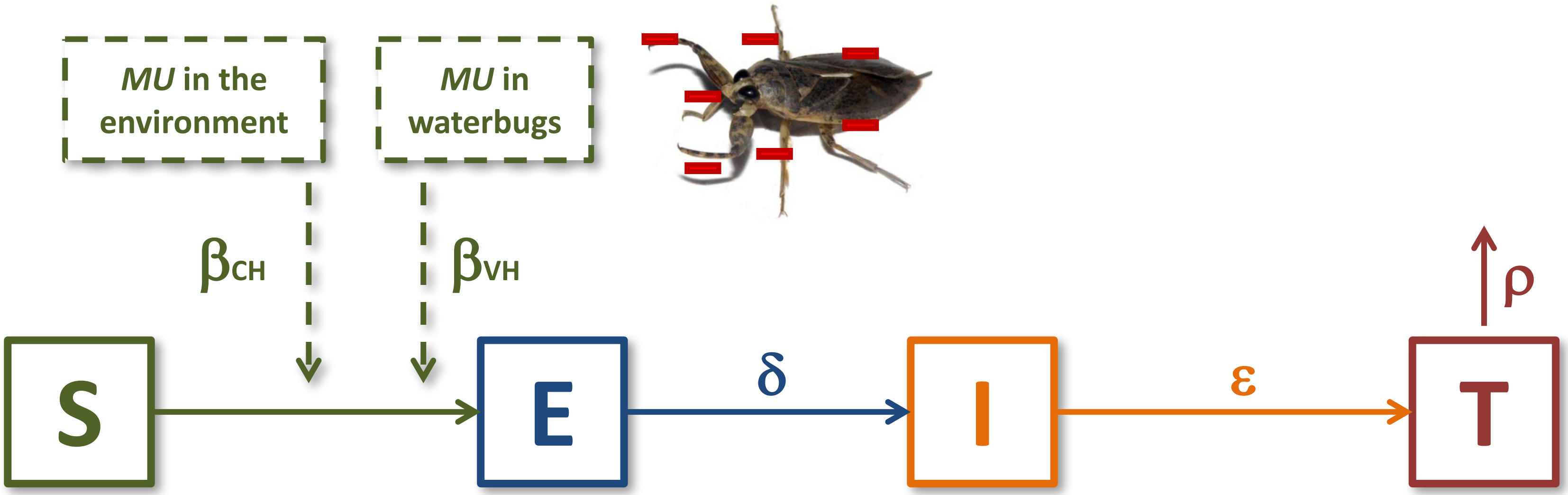
Transmission of MU to humans

3 Temporal data



3

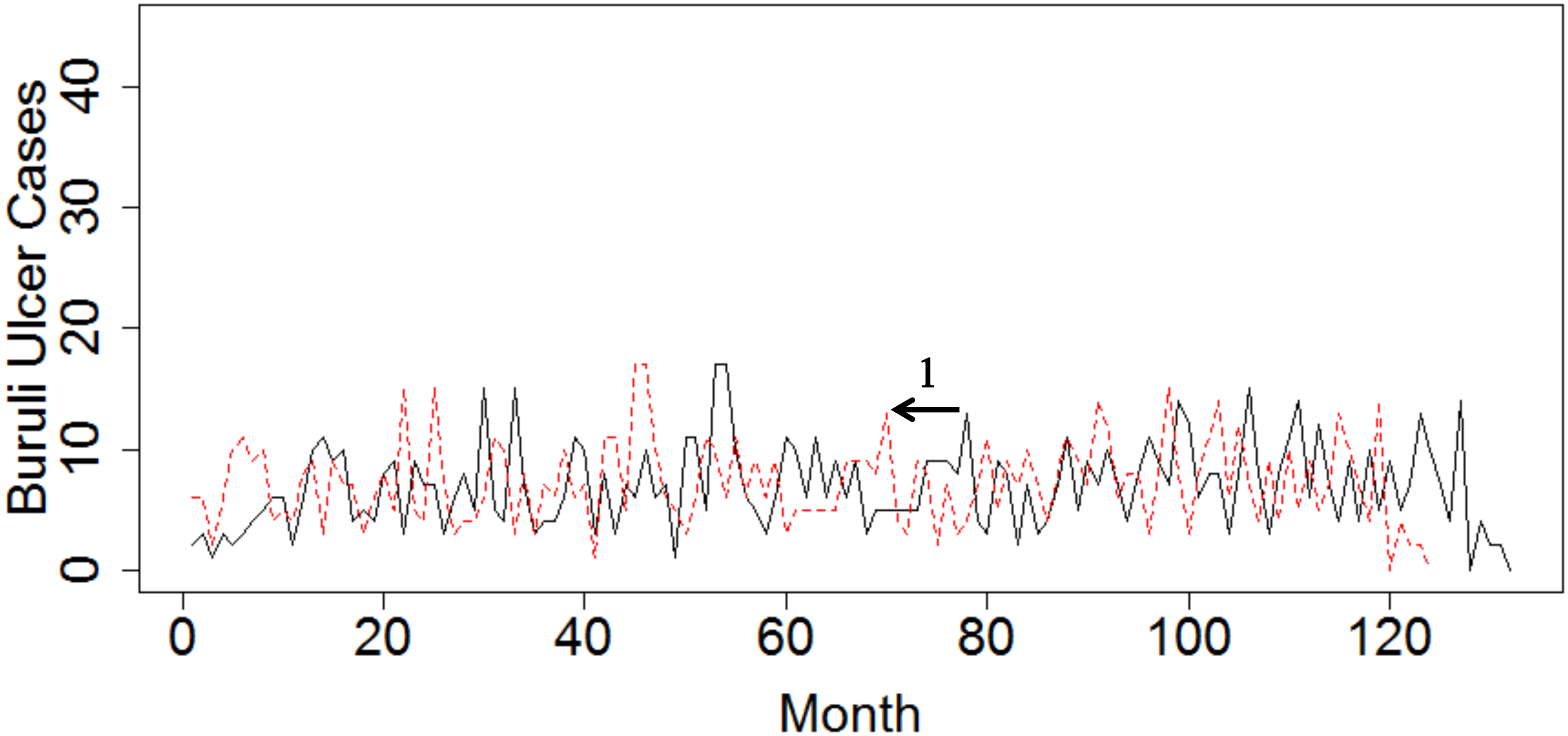
Mathematical model framework



Transmission of MU to humans

3 Estimation of Buruli ulcer cases (Temporal)

Incubation: 3 months
Time to seek treatment: 4 months



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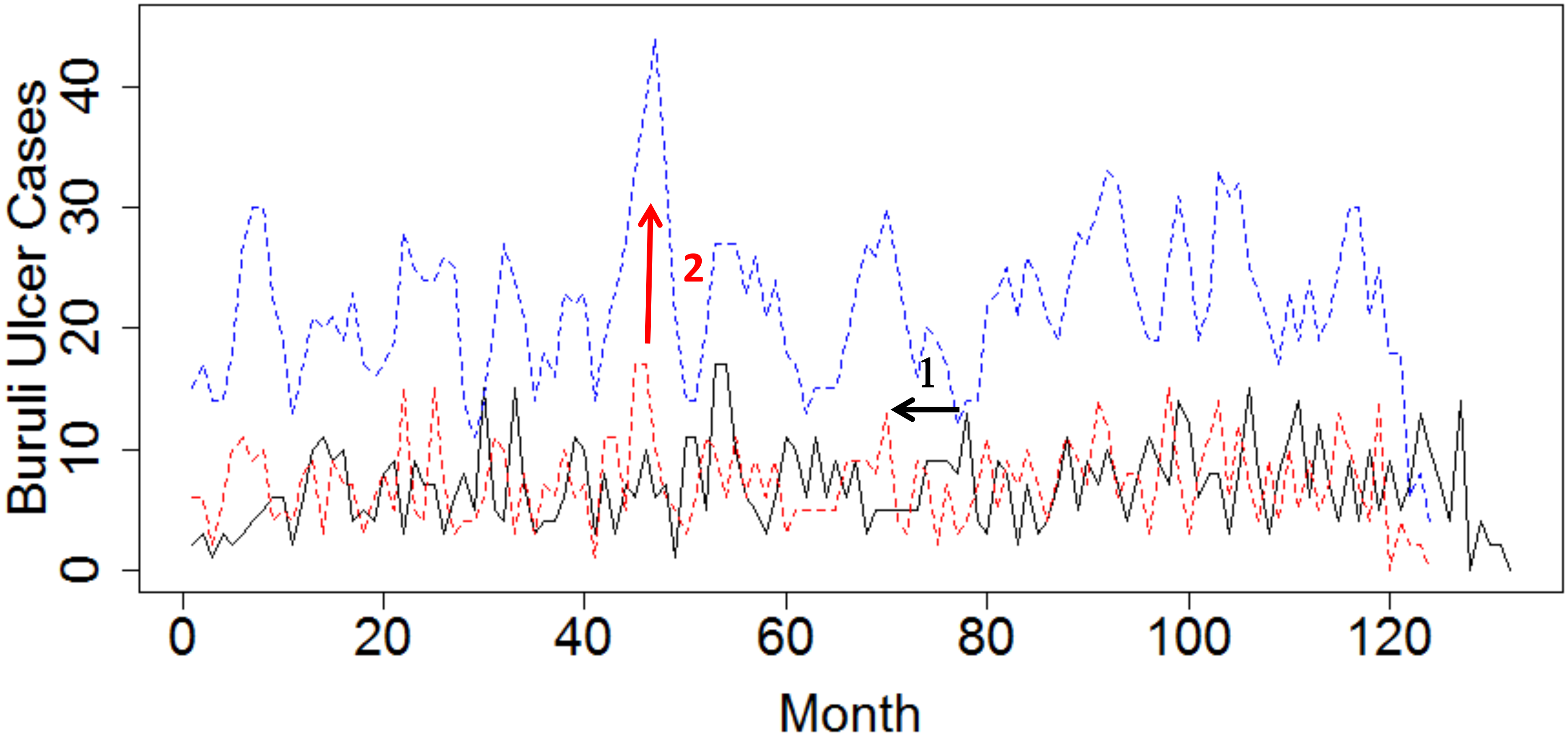

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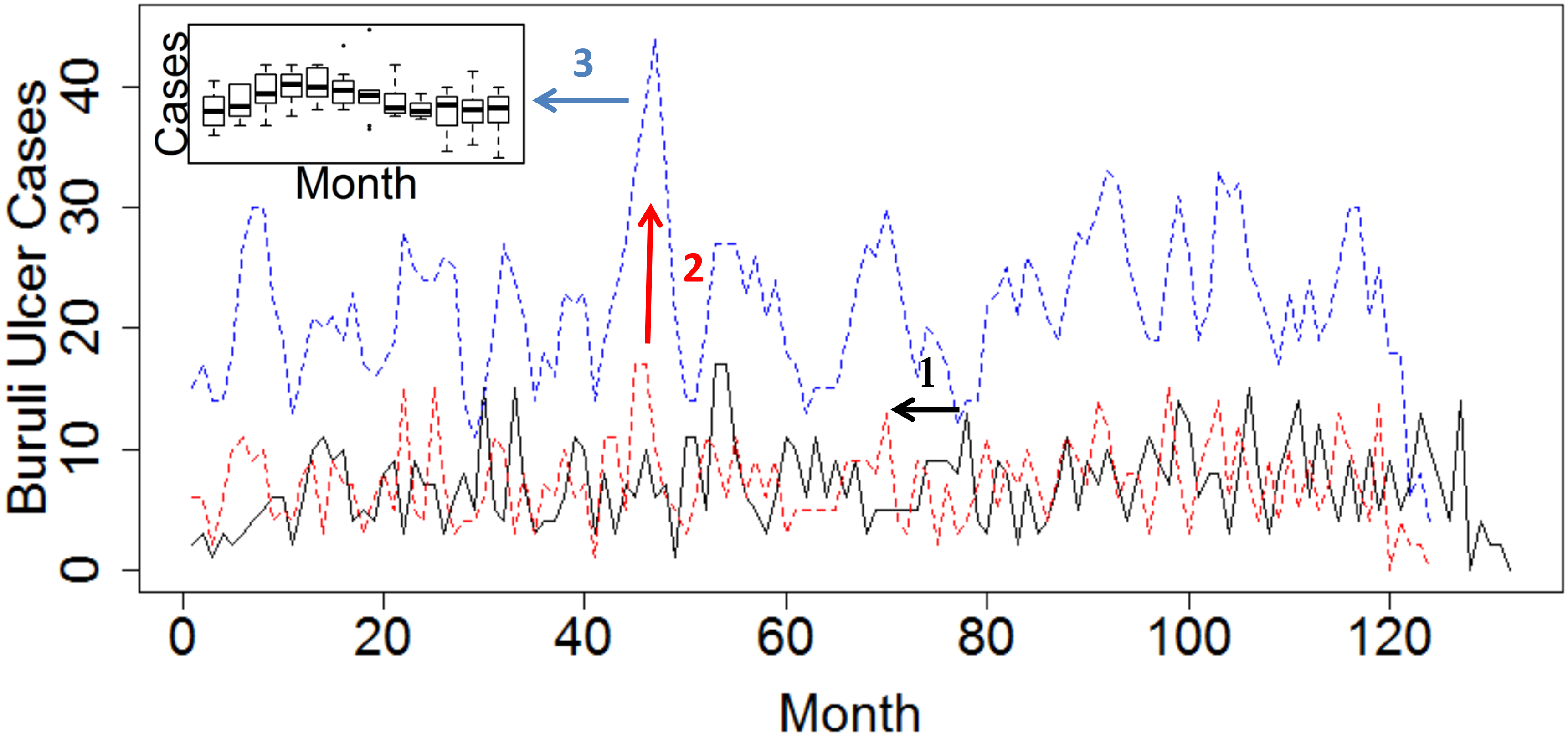
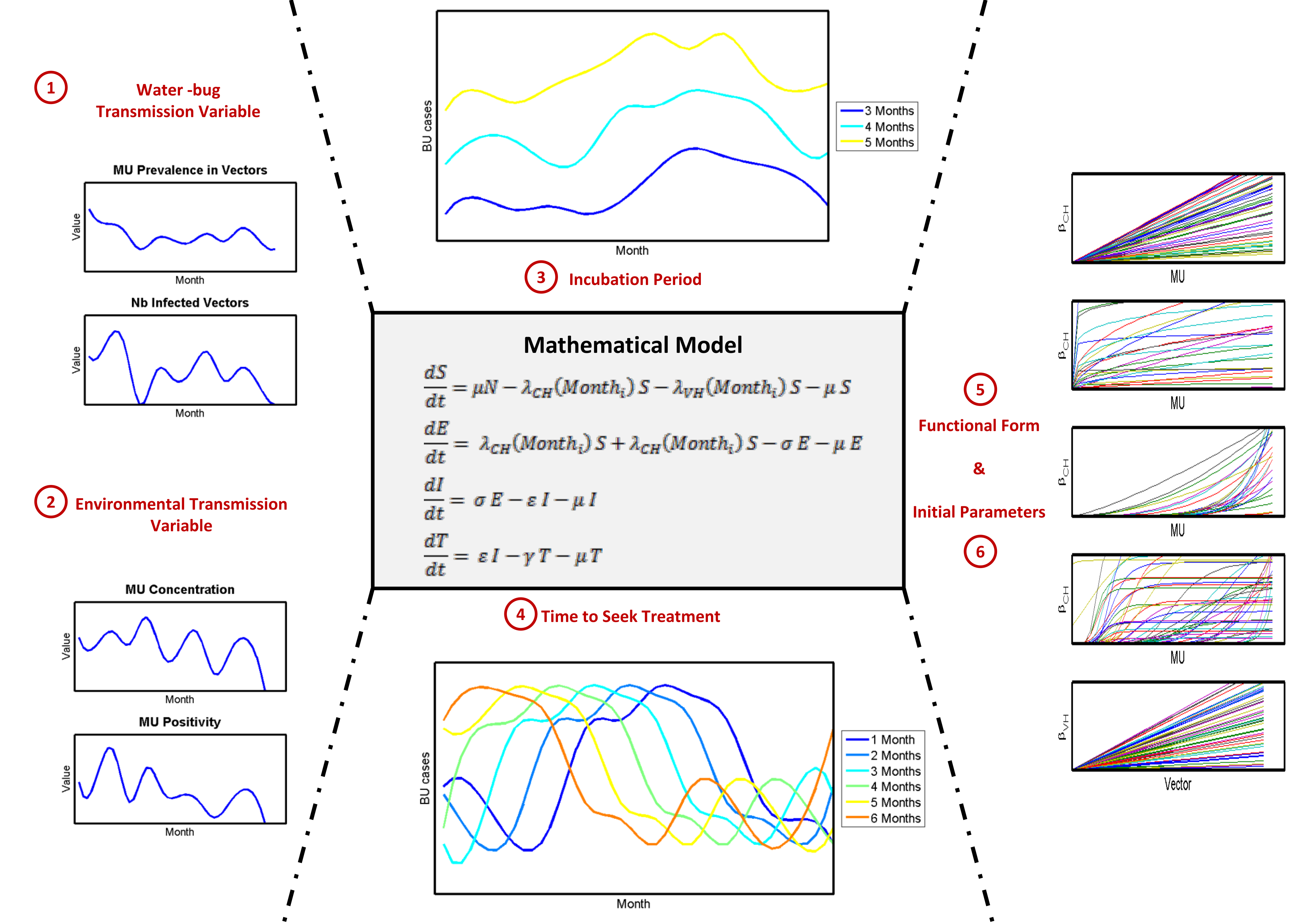


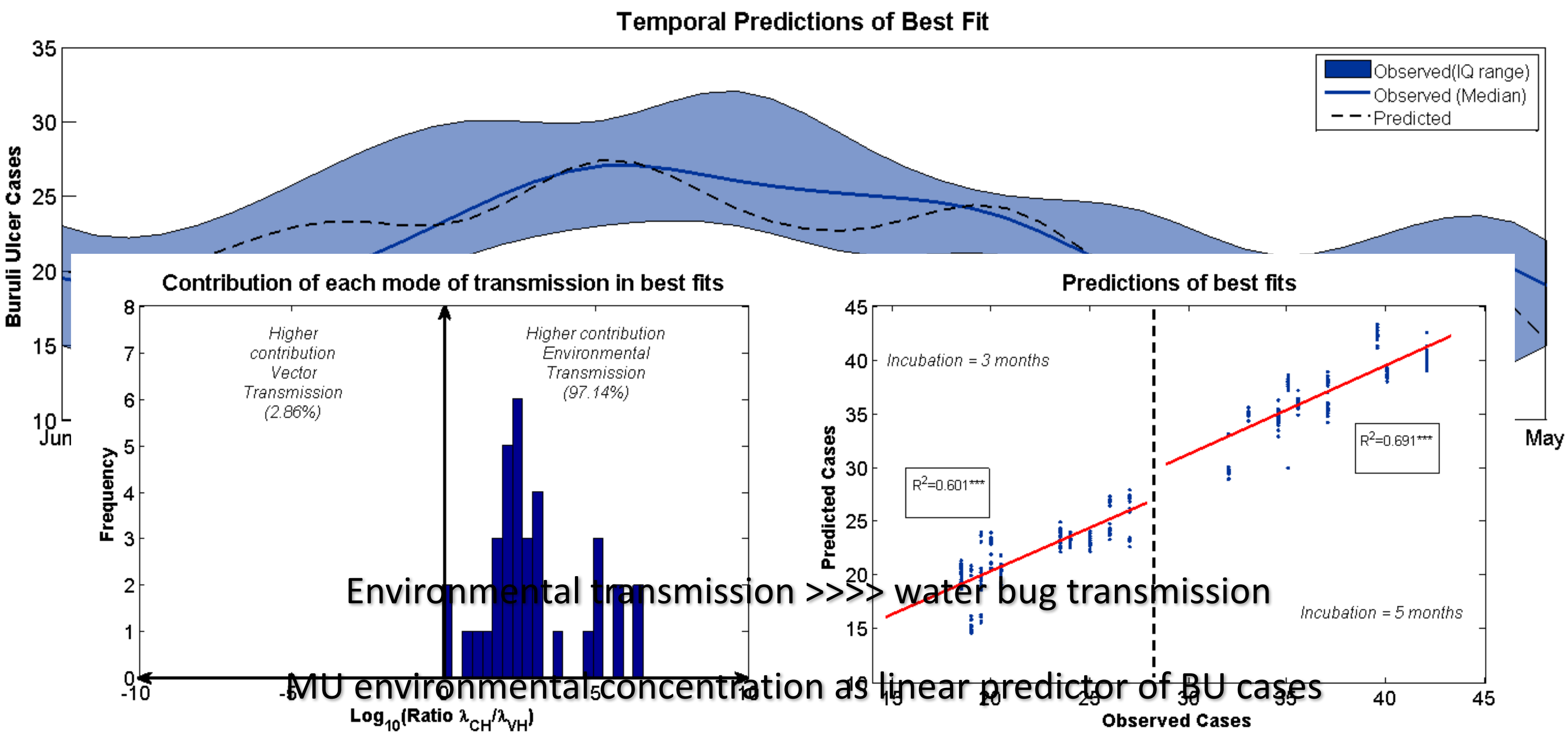


Transmission of MU to humans

3 Results for Buruli ulcer temporal dynamics

Best temporal fit

Variable	Relationship with BU	Time from Exposure to Treatment	Number of models	Mean λ_{CH}	Mean λ_{VH}	Mean AIC



Environmental transmission >>>> water bug transmission

MU environmental concentration as linear predictor of BU cases

CONCLUSIONS

Development of the study concept

- What is your question?
- Why is it interesting?
- Who is interested?
- Can it be narrowed down to a question about specific quantitative relationships?

Literature review

- Who has tried to answer this before and how did they do it?
  - Empirical studies
  - Modeling studies
- What are these studies short-comings?
- Are there already parameter estimates or data sets to help you answer your question?

Data collection

- What do you need to characterize?
  - Spatial and/or temporal dynamics
  - Relationships between parameters or systems

iv

Construction of model framework

- What drawbacks of previous studies can I mitigate?
- What type of modeling is necessary to answer my question?
    - Statistical: GLM, spatial, time-series, etc.
    - Mathematical: population based, individual based
- What modeling elements are necessary for my question?
    - Stochasticity
    - Compartments and complexity

V

Model analysis, selection and validation

- What model(s) best fit my data and explain my question?
  - Comparison of alternative models and application of selection procedures
- Does the selected model suffer from any substantial drawbacks?
  - Statistical models: verification of model assumptions
  - Mathematical models: sensitivity analyses and out-of-sample predictions

vi Manuscript writing and submission

- What are the main results that provide the answer to my question?
  - 1 to 3 graphs
  - 1 to 3 tables
- What is the journal that best fits my study?
  - Scope, audience, impact factor, math focus
- How do I present my manuscript?
  - Introduction: set the stage to your question
  - Methodology: describe explicitly all steps for replicability
  - Results: clear and concise
  - Discussion: explain how your study improves previous knowledge

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- The example of Buruli ulcer in Cameroon -

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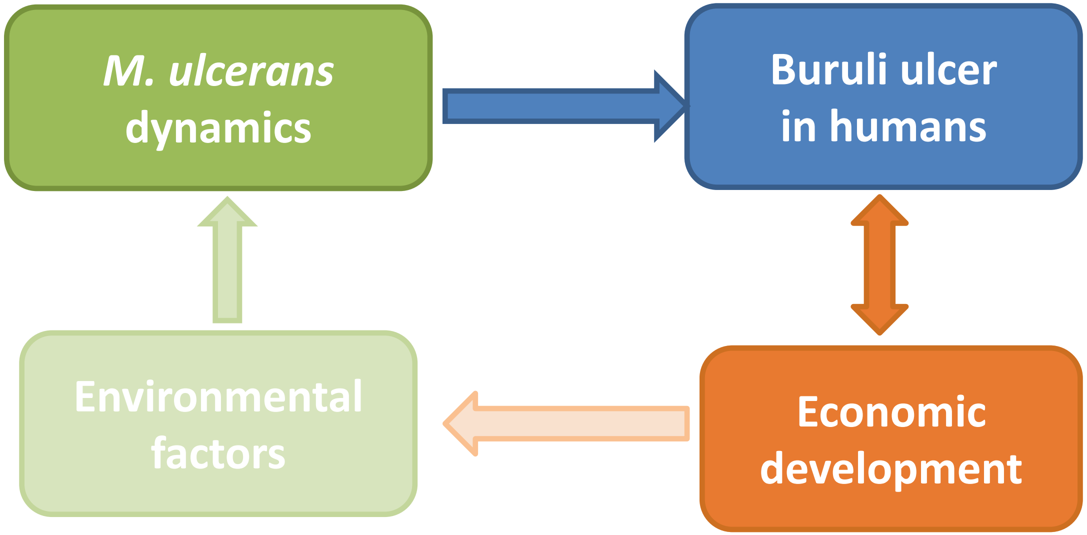
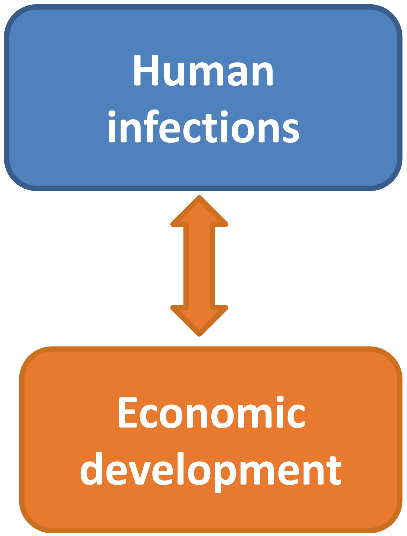
E²M² Workshop
Ranomafana, November 2016

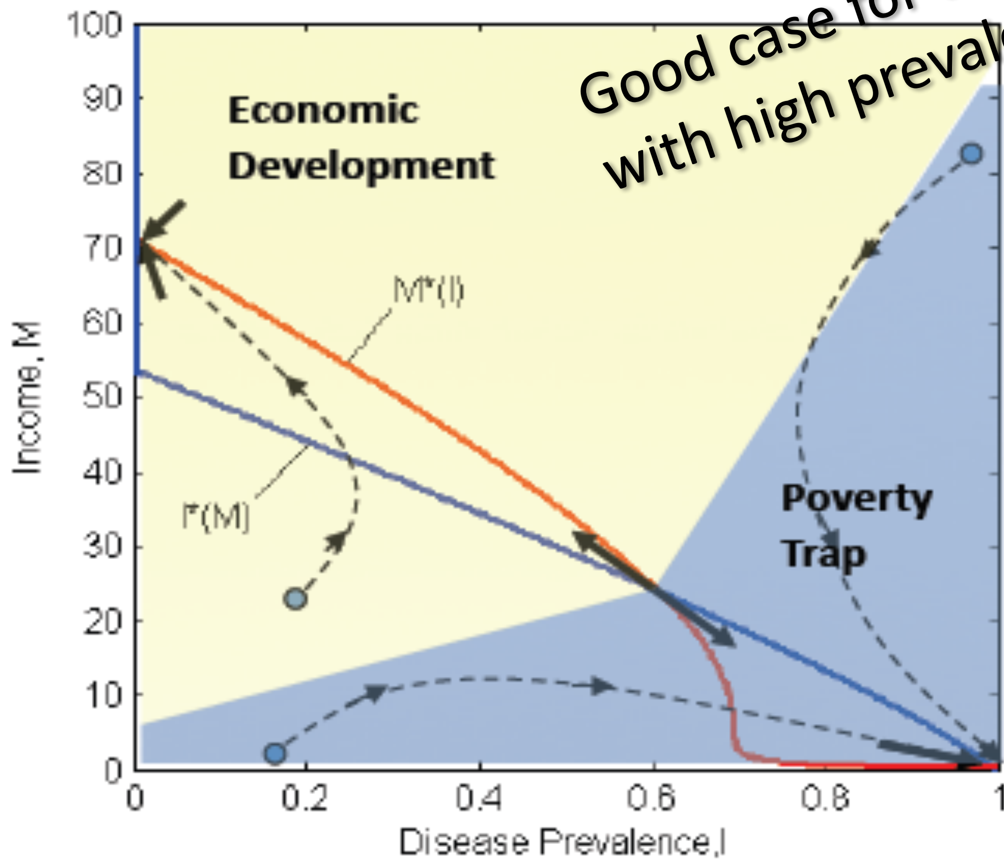


6. THEORETICAL MODELS TO UNDERSTAND FEEDBACKS WITH POVERTY



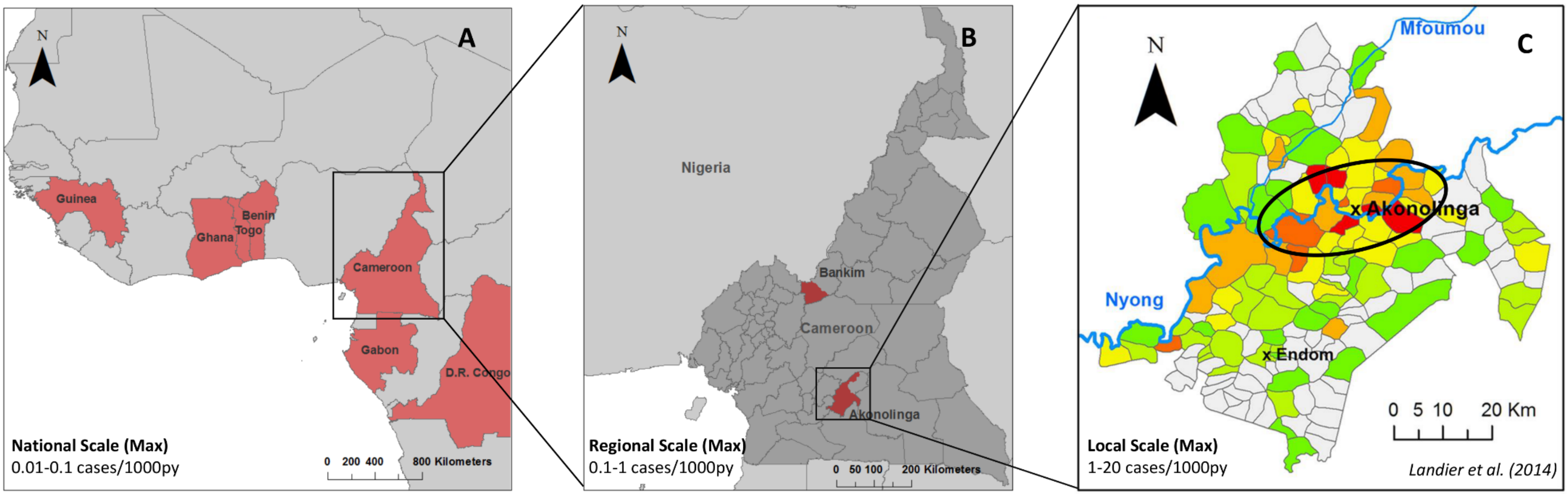
What about rare diseases like BU?

Good case for diseases with high prevalence



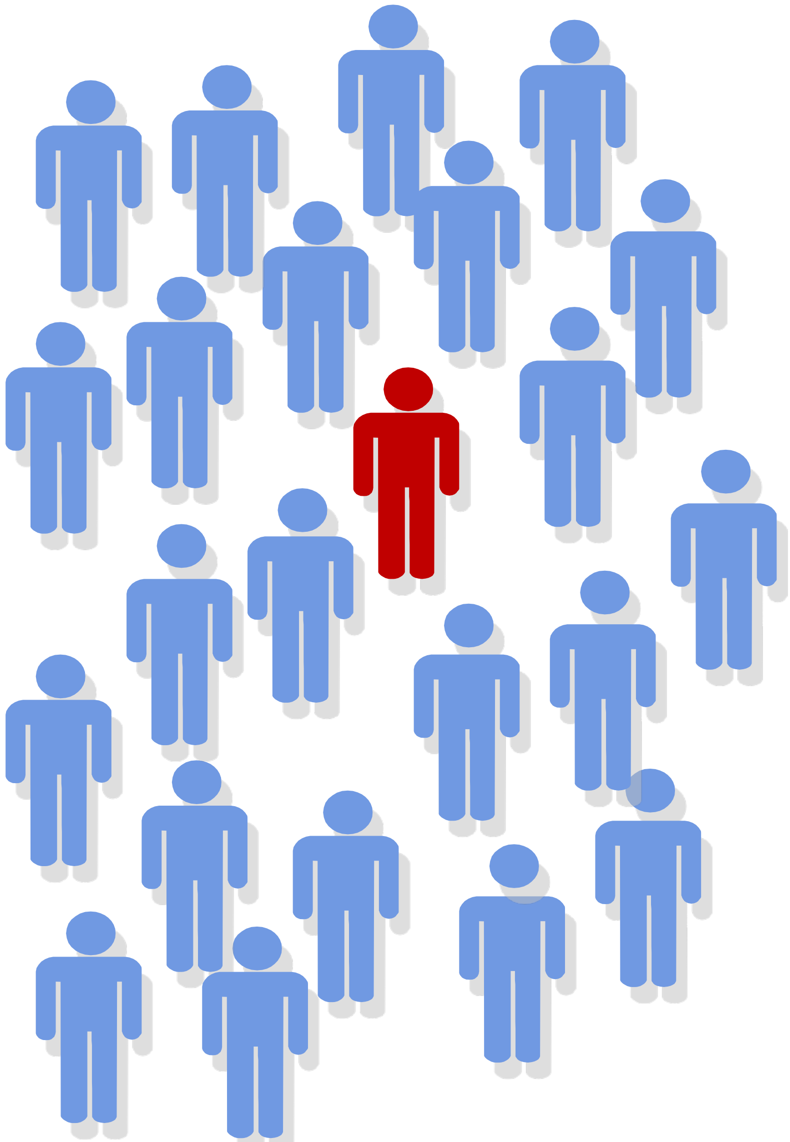
Poverty Trap Formed by the Ecology of Infectious Diseases
Bonds, Keenan, Rohani and Sachs (2009)

4 Introduction



4

Introduction



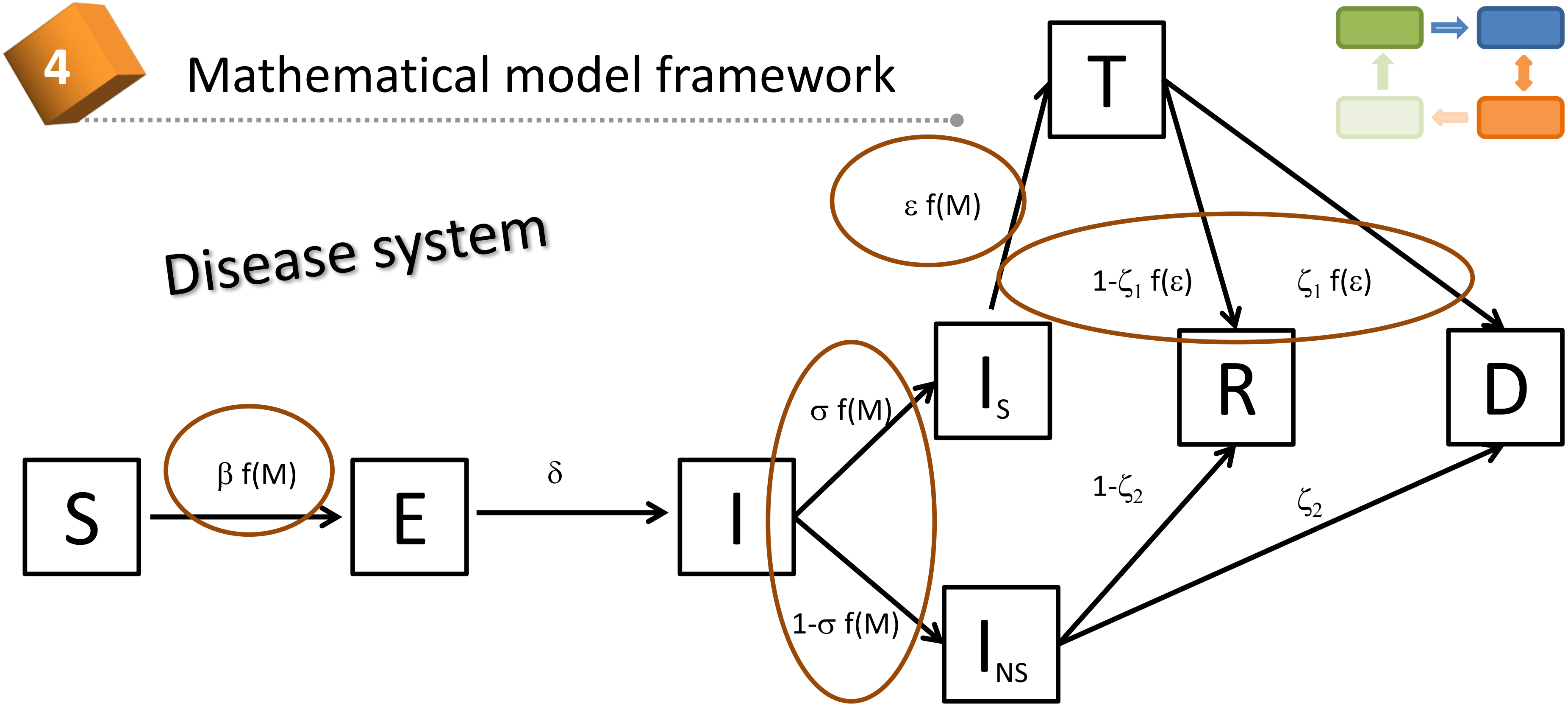
Population-based models

Tracks mean changes in the population

Individual-based models

Tracks information about each individual

4 Mathematical model framework



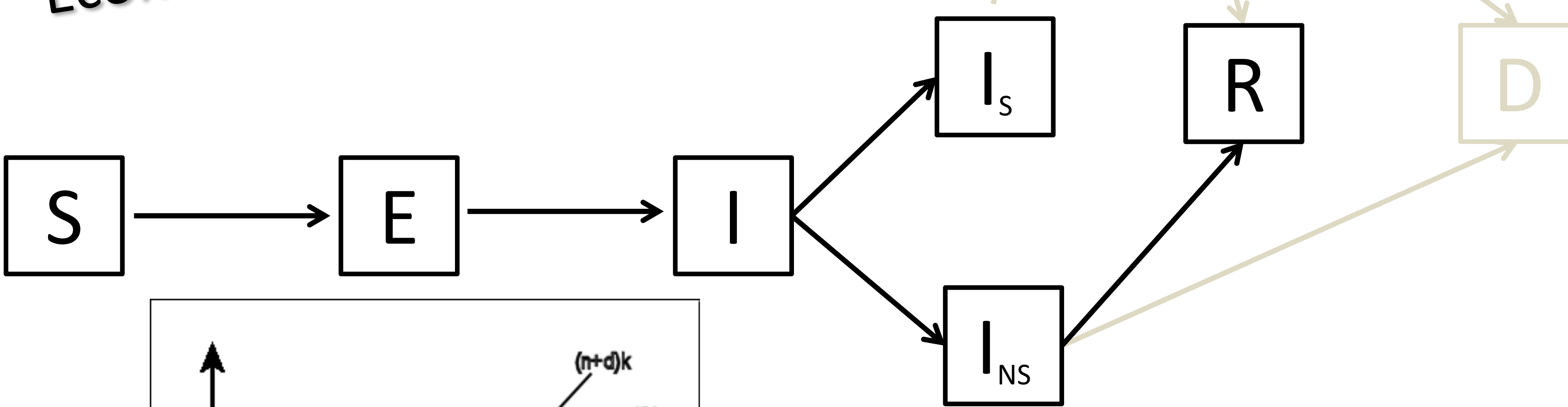
Transmission probability (β), probability and time to seek treatment (σ,ε) are a function of capital (M)

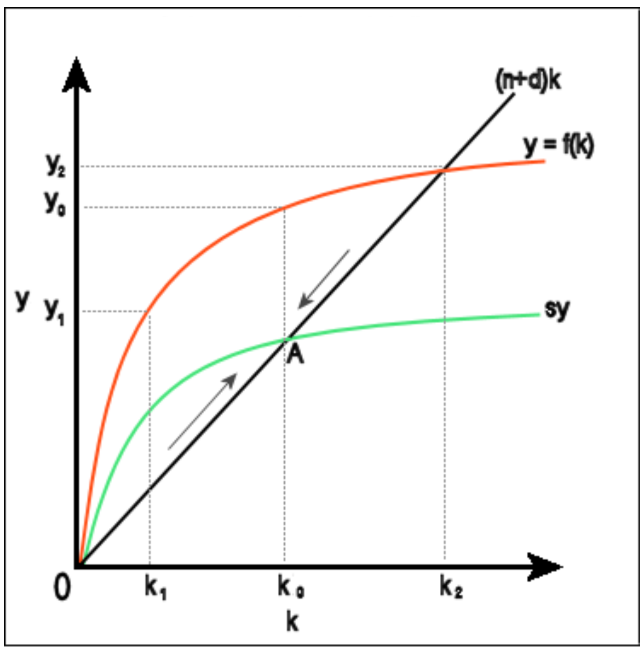
Recovery rate and probability of functional limitations (ζ) are a function of the time to seek treatment (1/ε)

4

Mathematical model framework

Economic growth system

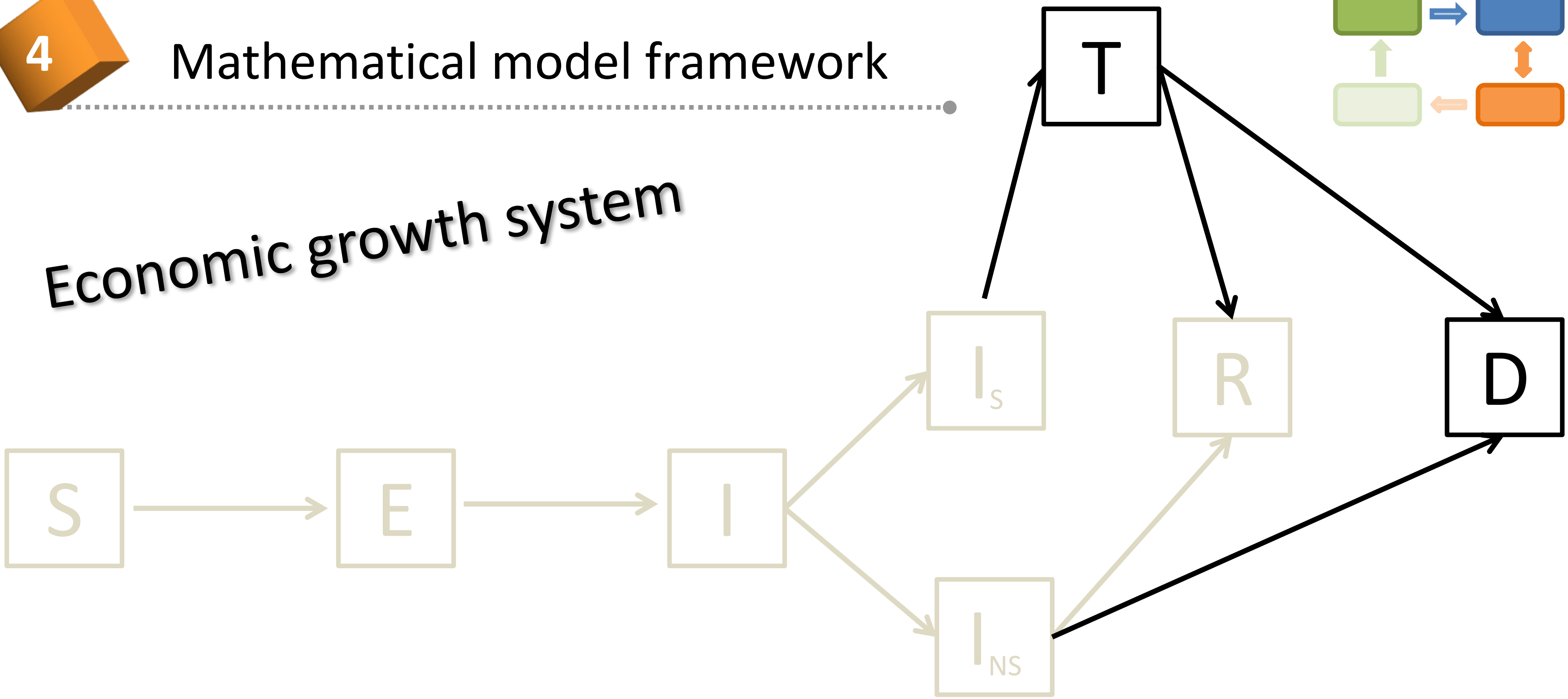




Exponential growth

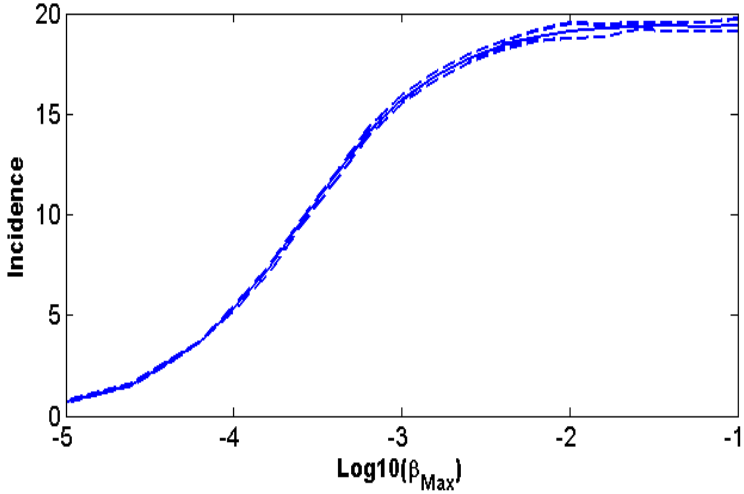
Mathematical model framework

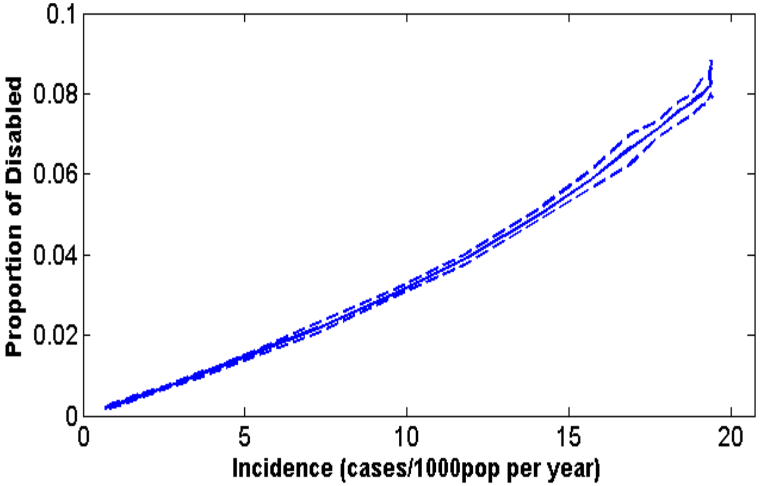
Economic growth system

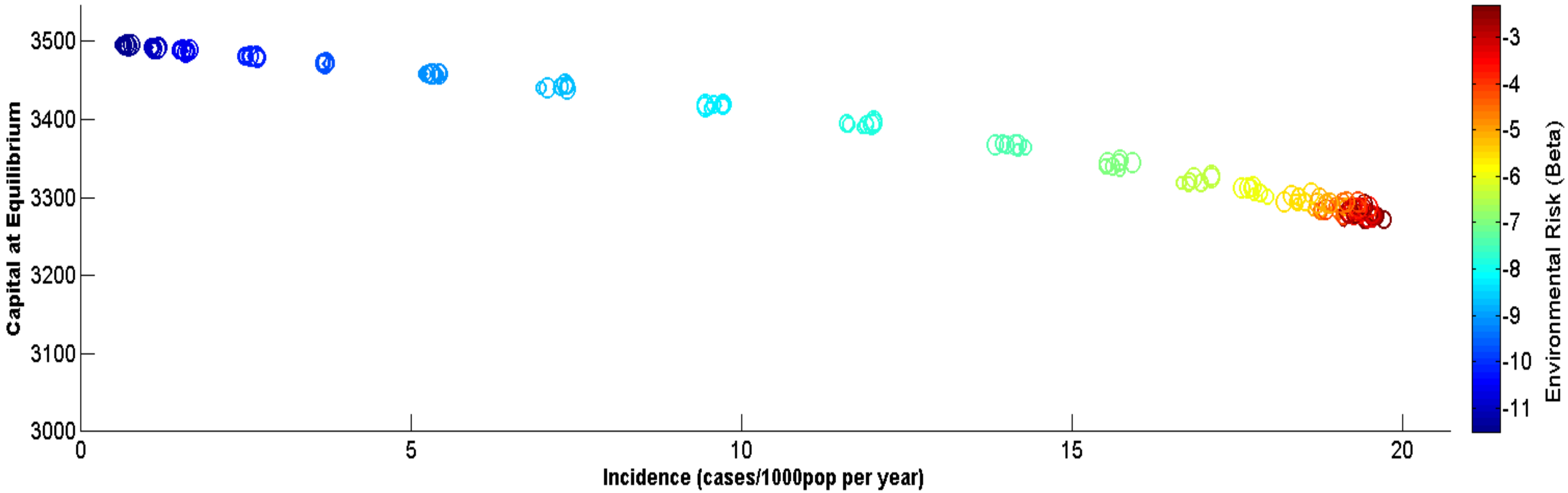


Cost of treatment
&
Loss of productivity

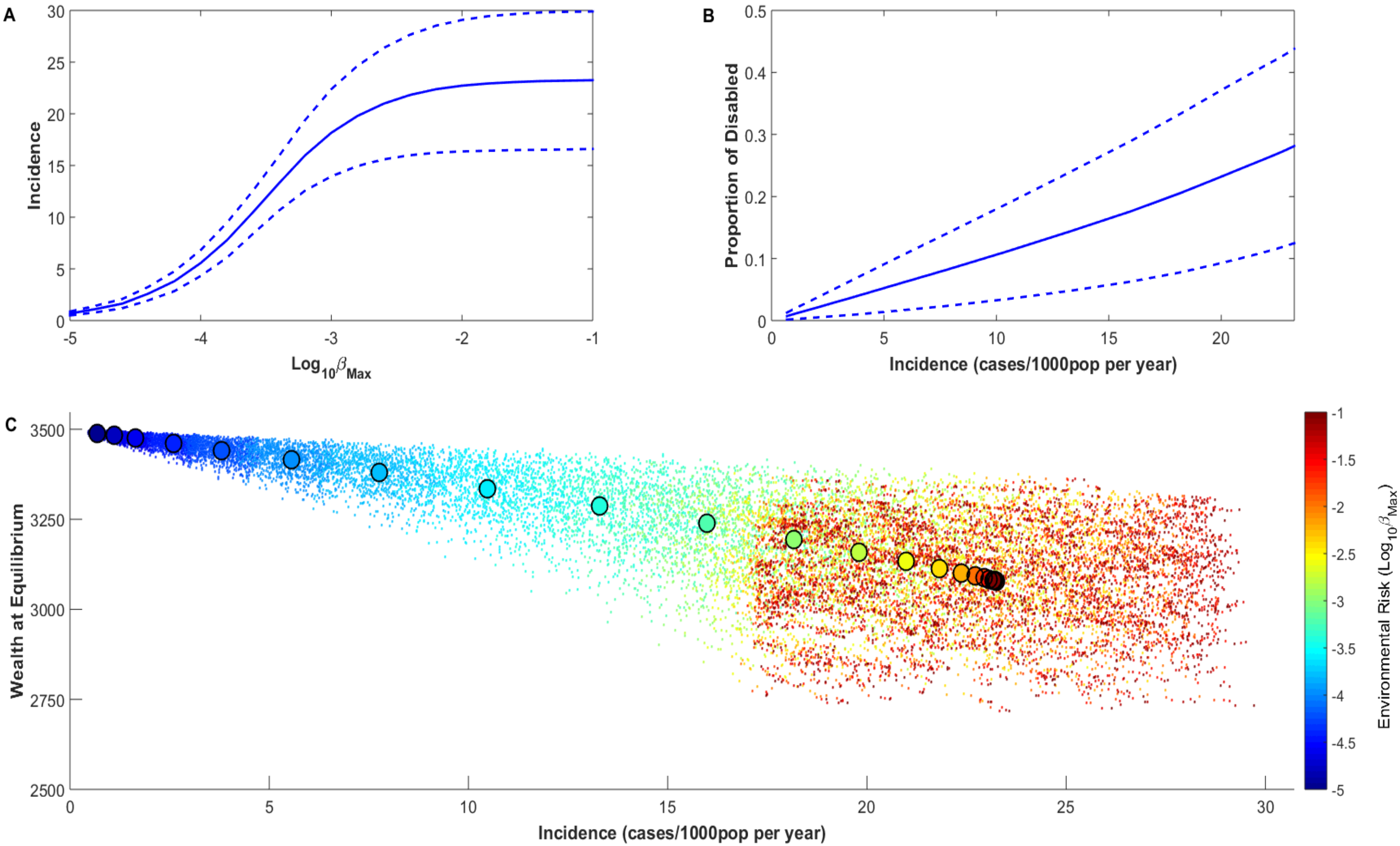
Mean results for the whole population



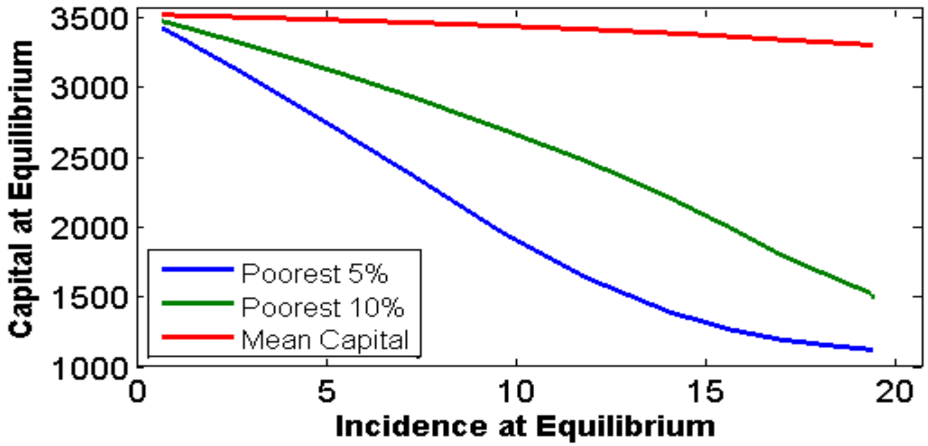


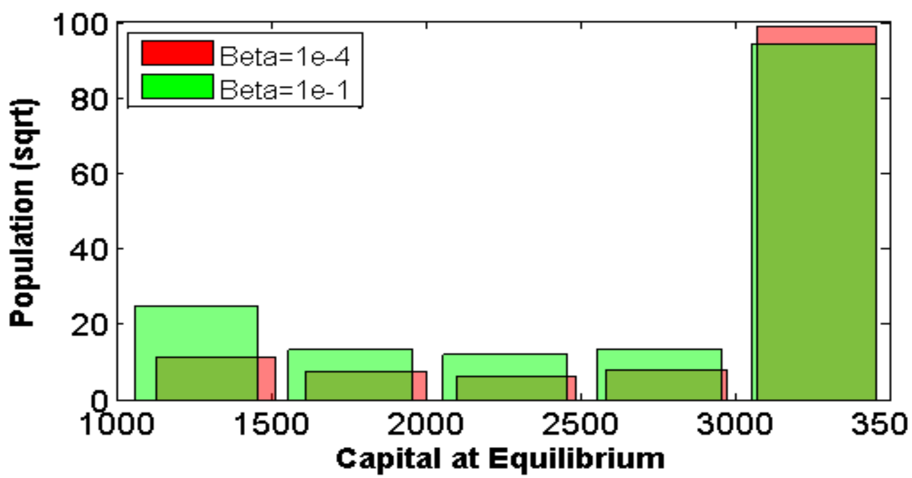


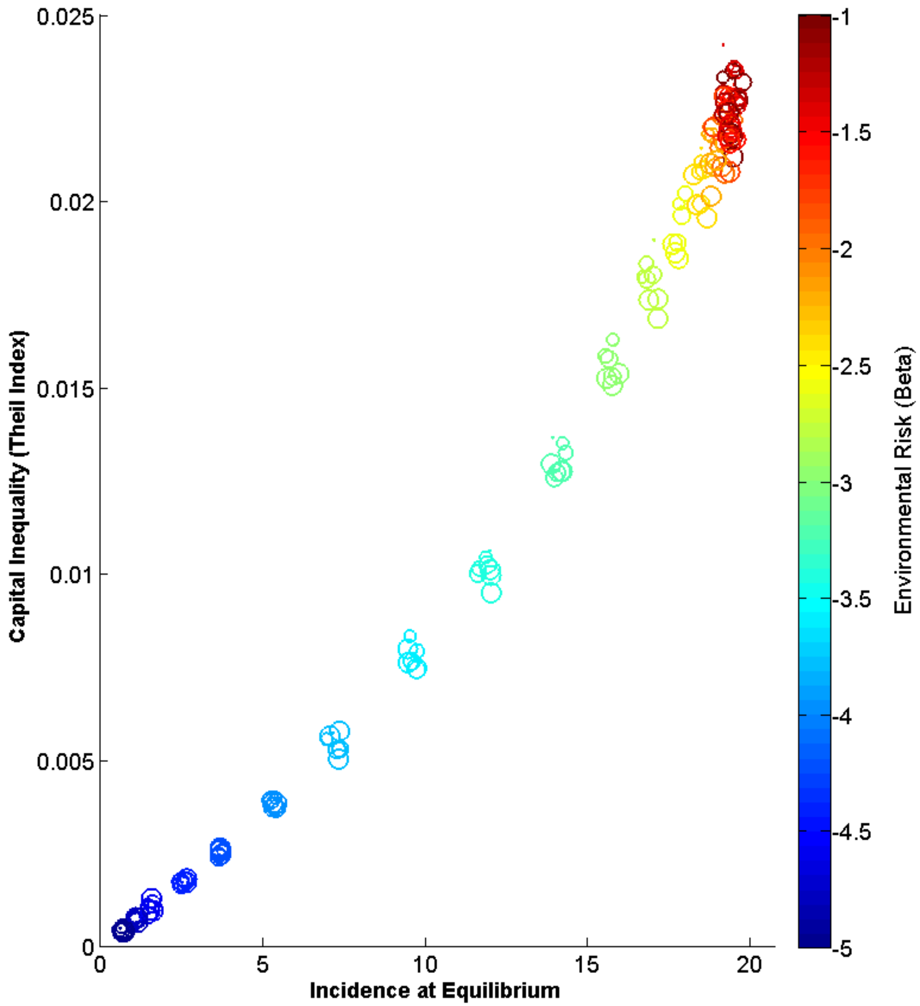
4 Mean results for the whole population



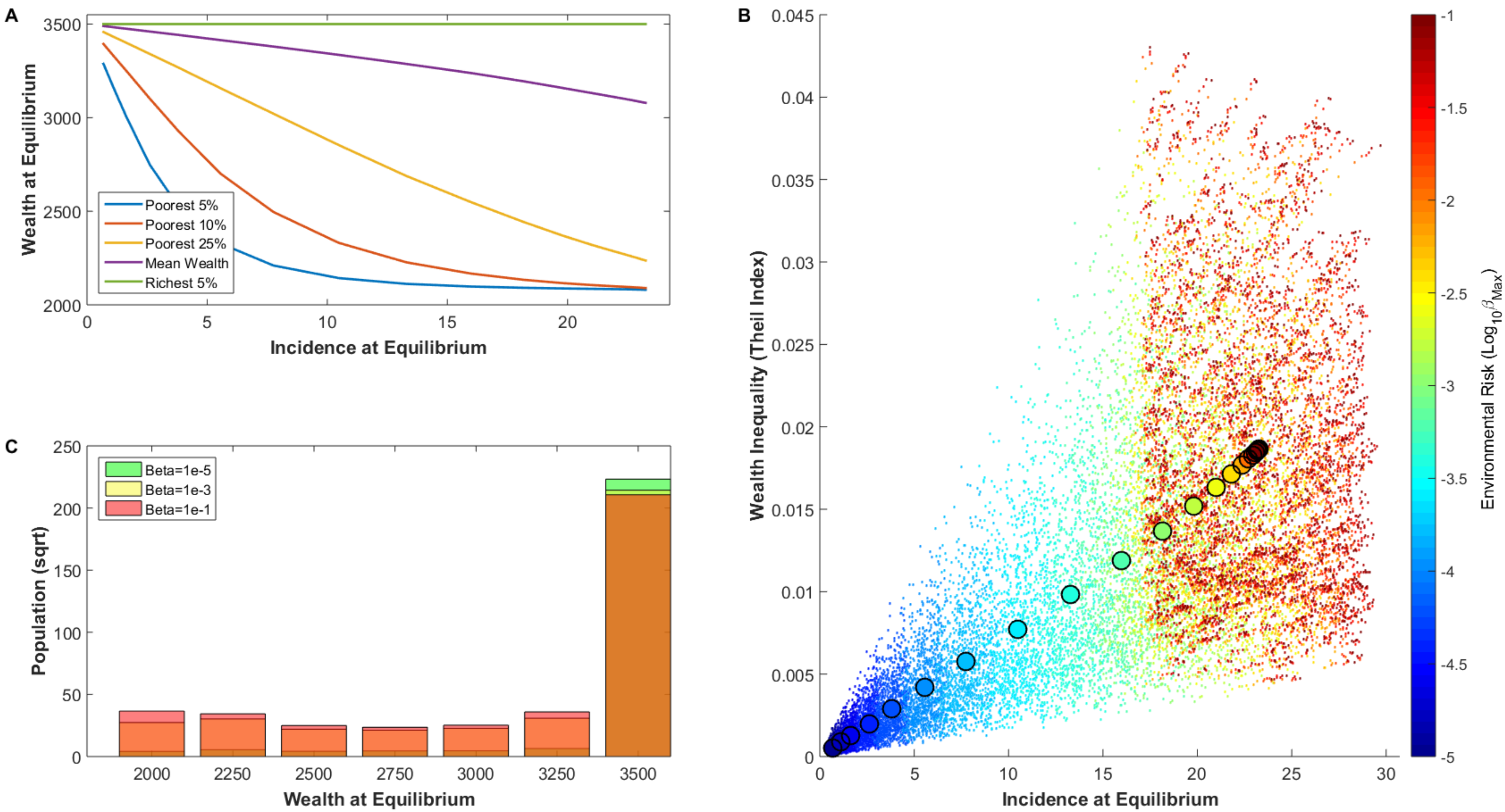
Results for subgroups of the population



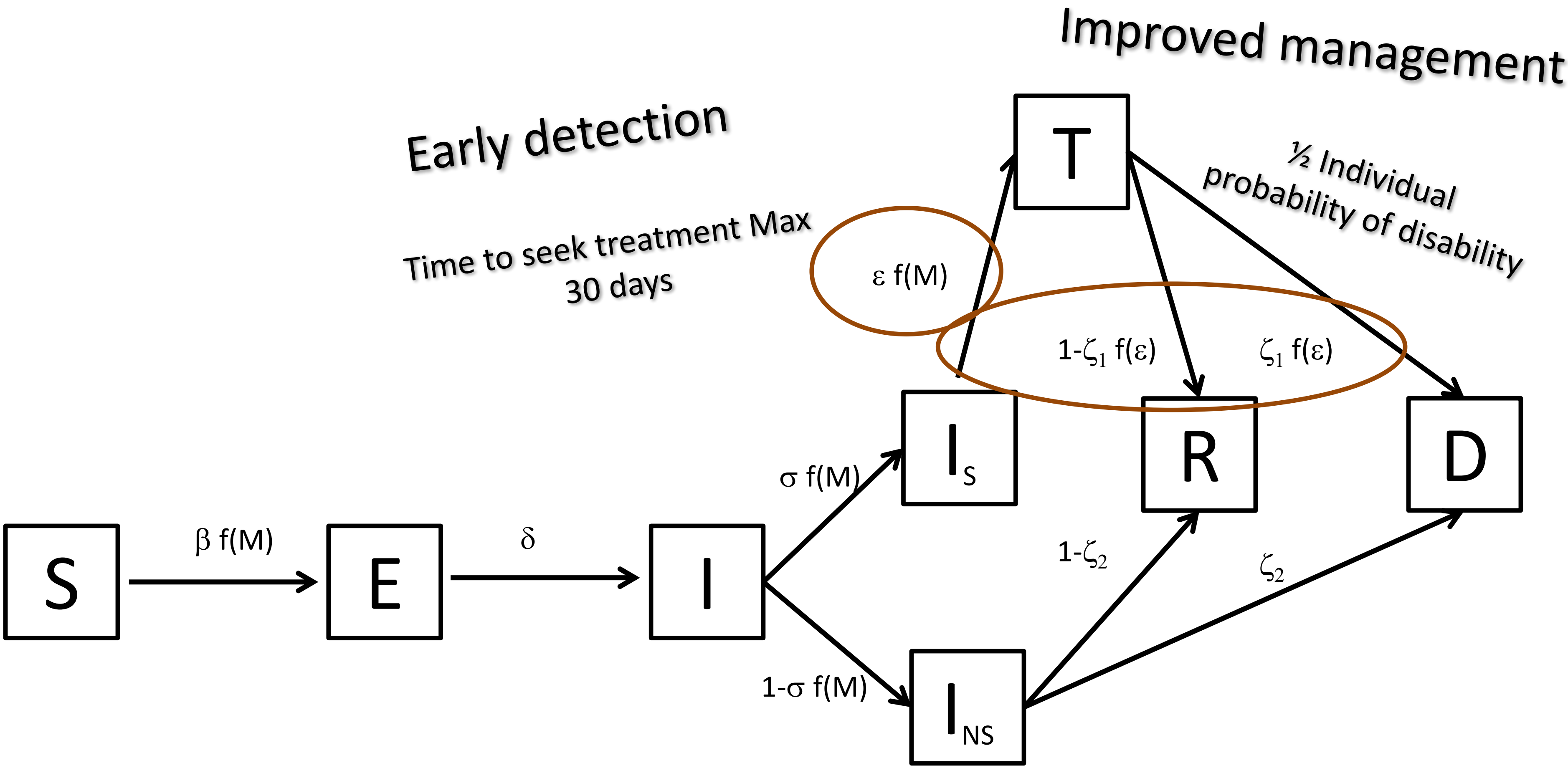




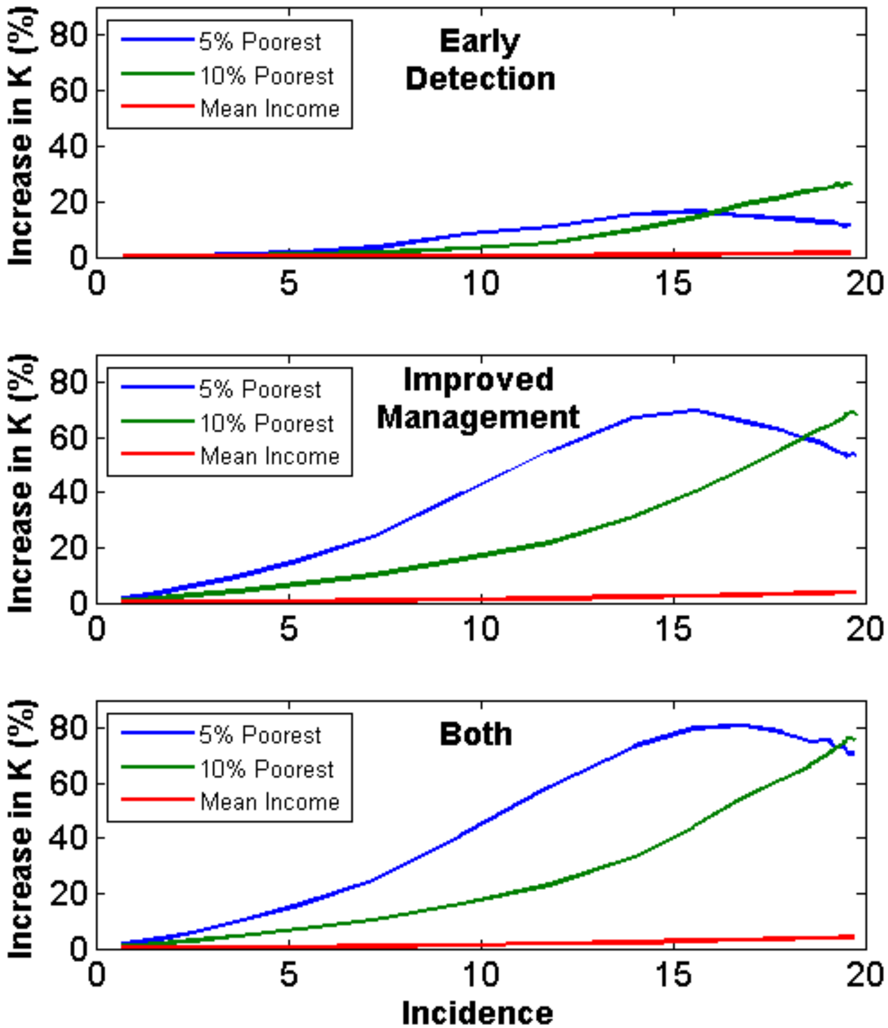
4 Results for subgroups of the population

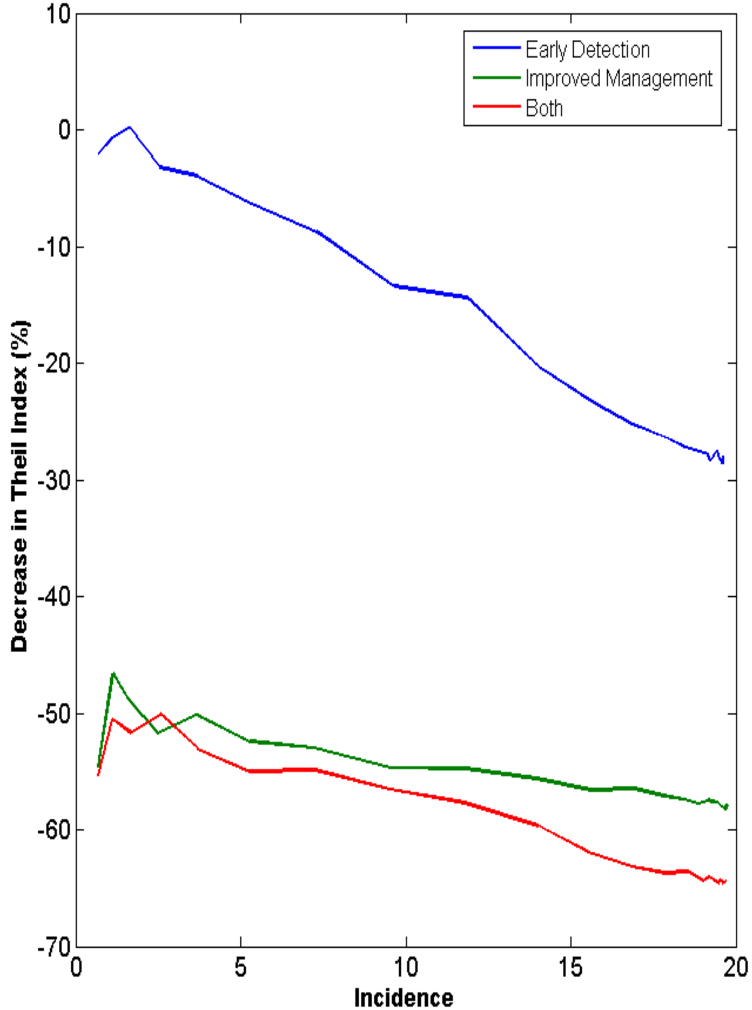


4 Impact of strategies for disease control



Impact of strategies for disease control





4 Impact of strategies for disease control