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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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*

Development of the study concept

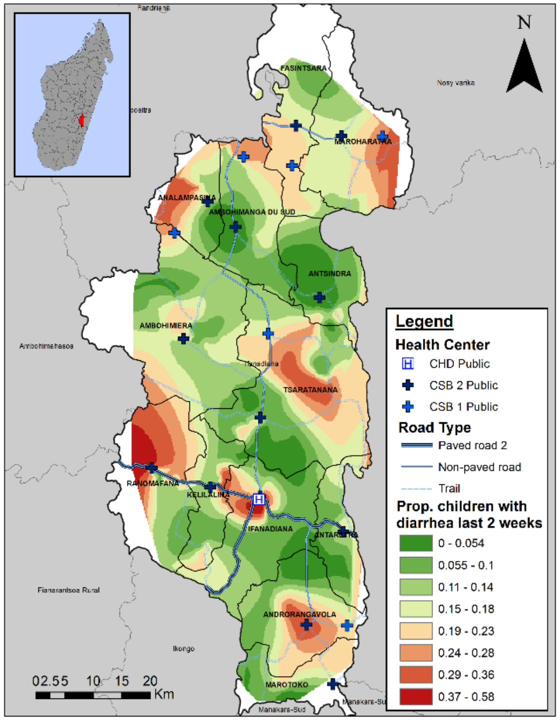
- What is your question?
- Why is it interesting?
- Who is interested?
- Can it be narrowed down to a question about specific quantitative relationships?

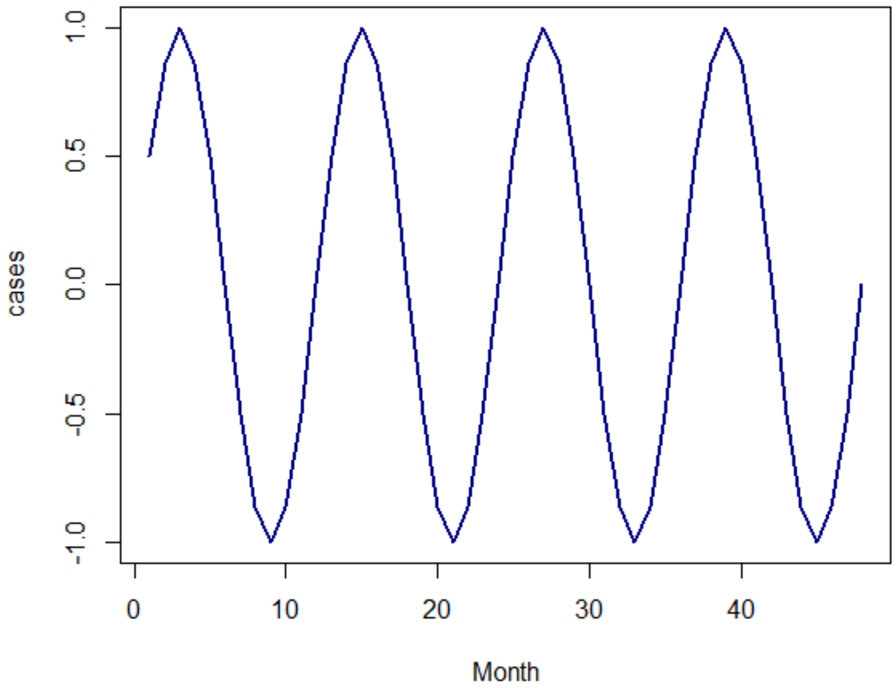
Literature review

- 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

Data collection

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





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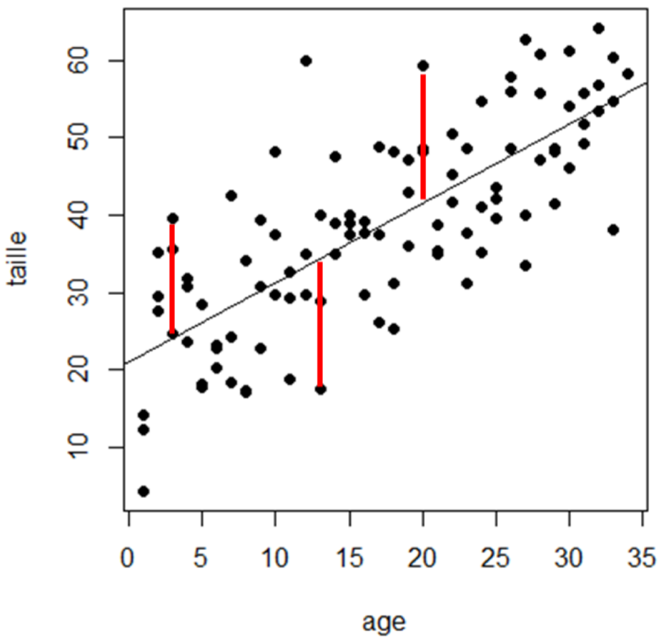
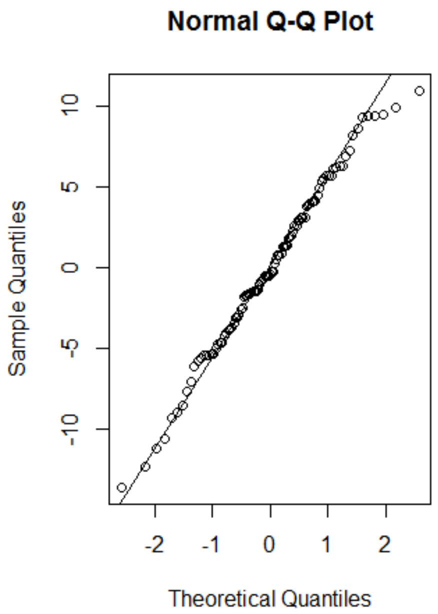
Construction of model framework

- 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

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





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

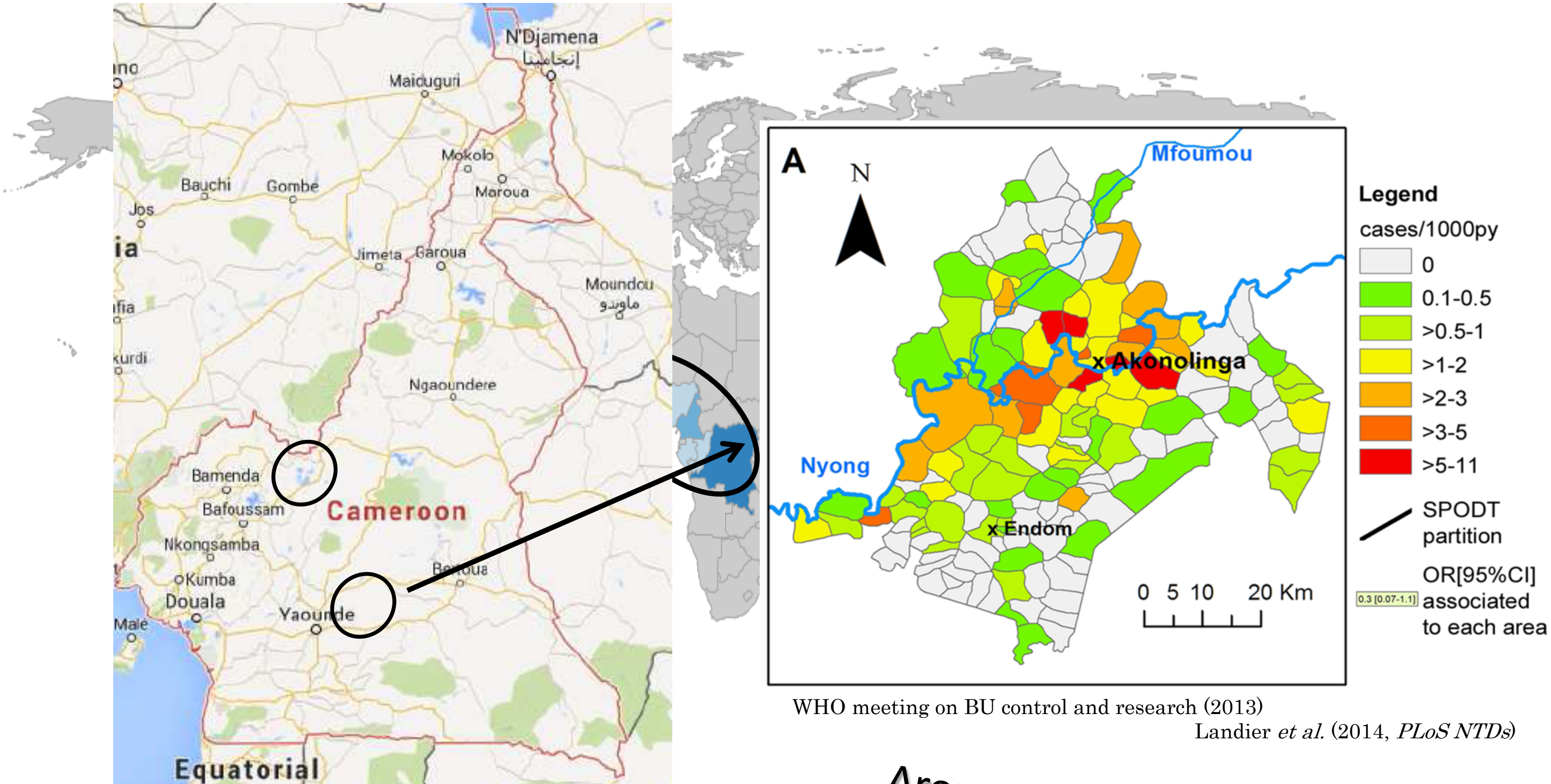
Buruli ulcer

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

What is my question?

Why is it interesting?

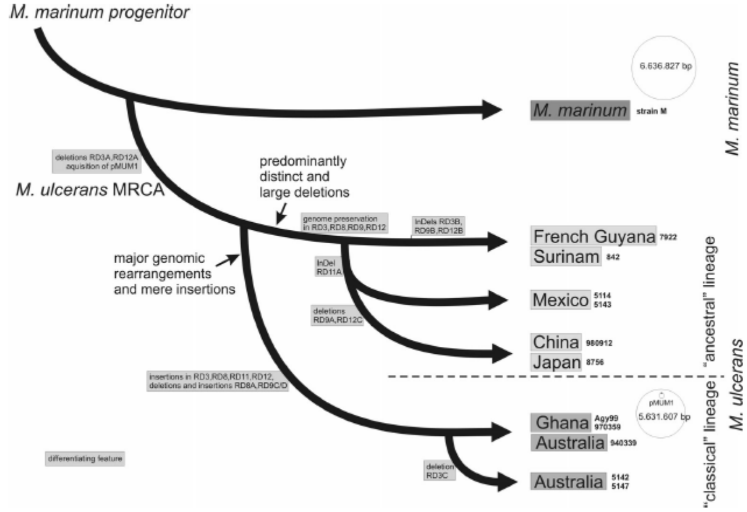
Who has tried to answer this before and how?

What are these studies short-comings?

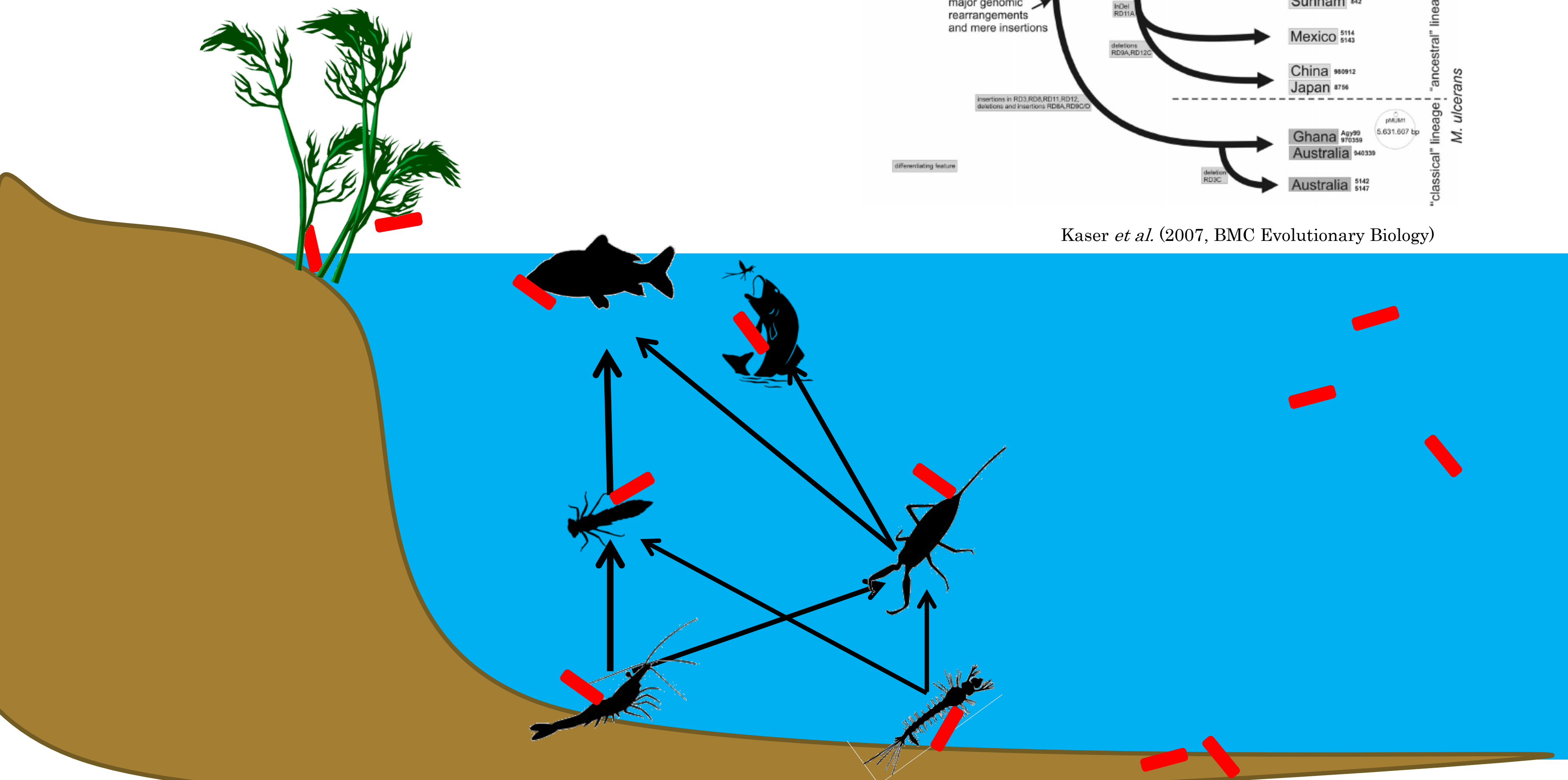
1. LITERATURE REVIEW
&
IDENTIFICATION OF THE PROBLEM

Mycobacterium ulcerans: generalities

Multi-host
&
Environmentally persistent



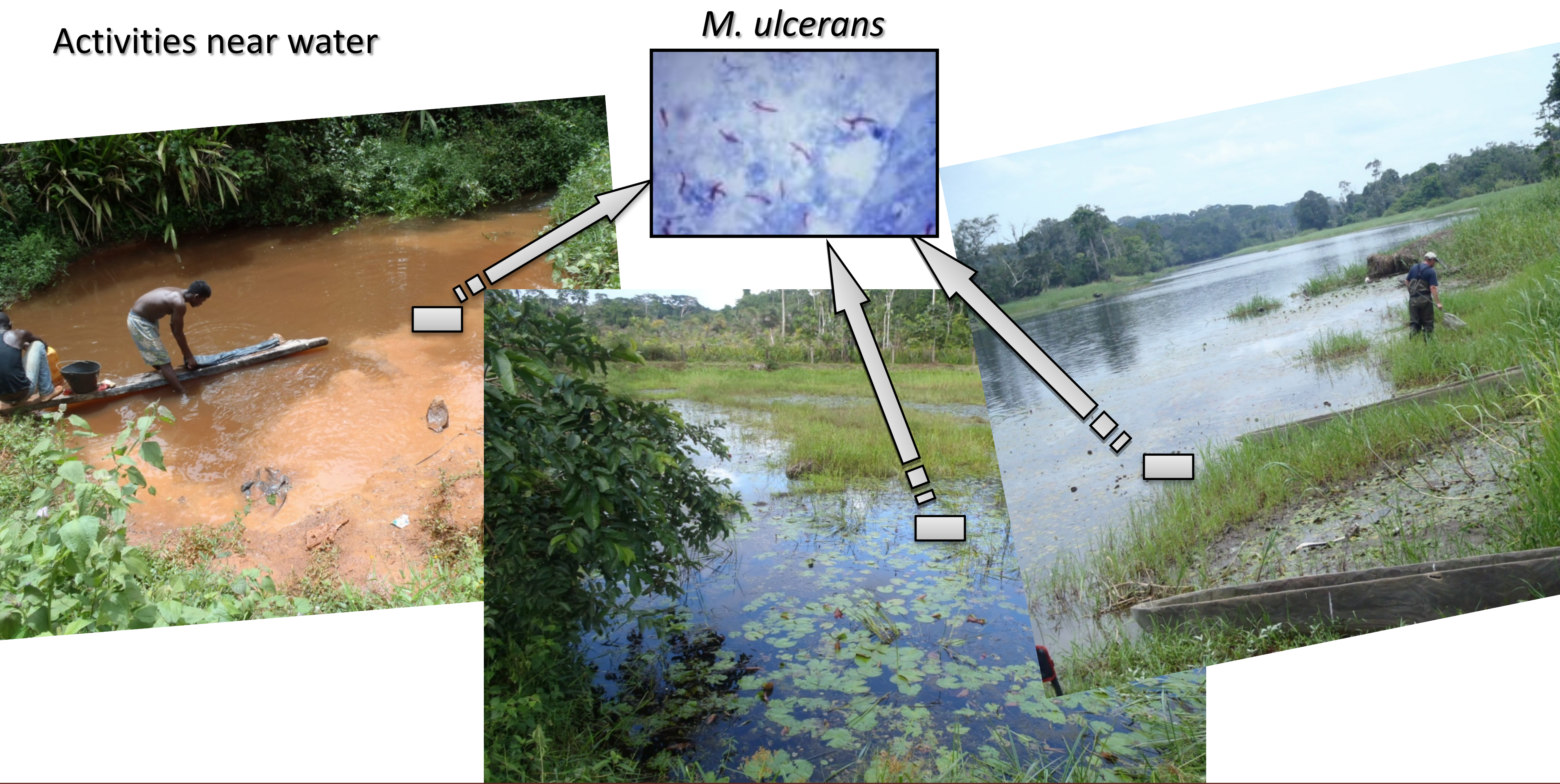
Kaser *et al.* (2007, BMC Evolutionary Biology)



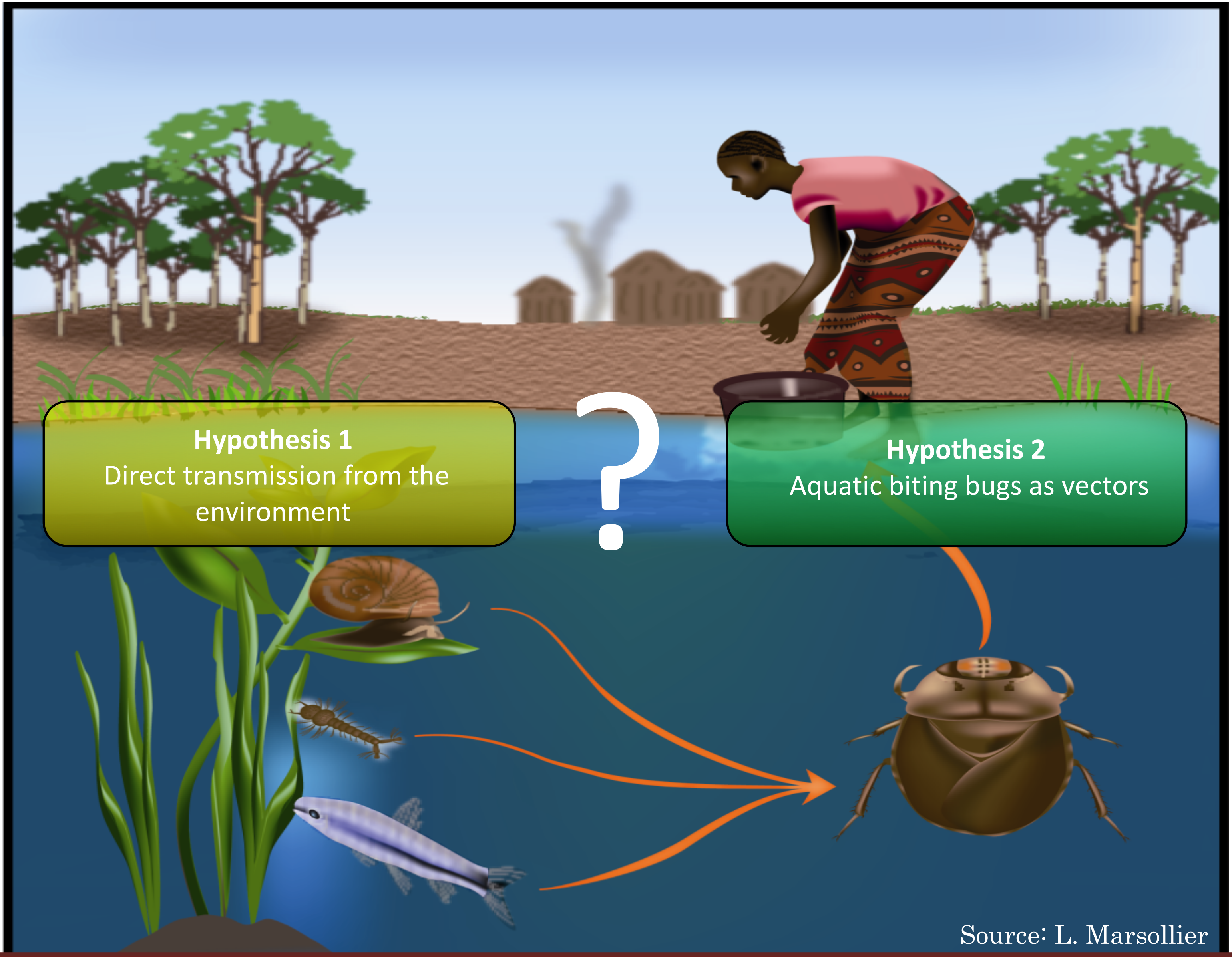
BU Risk factors

Proximity to stagnant or slow flowing waters

Activities near water



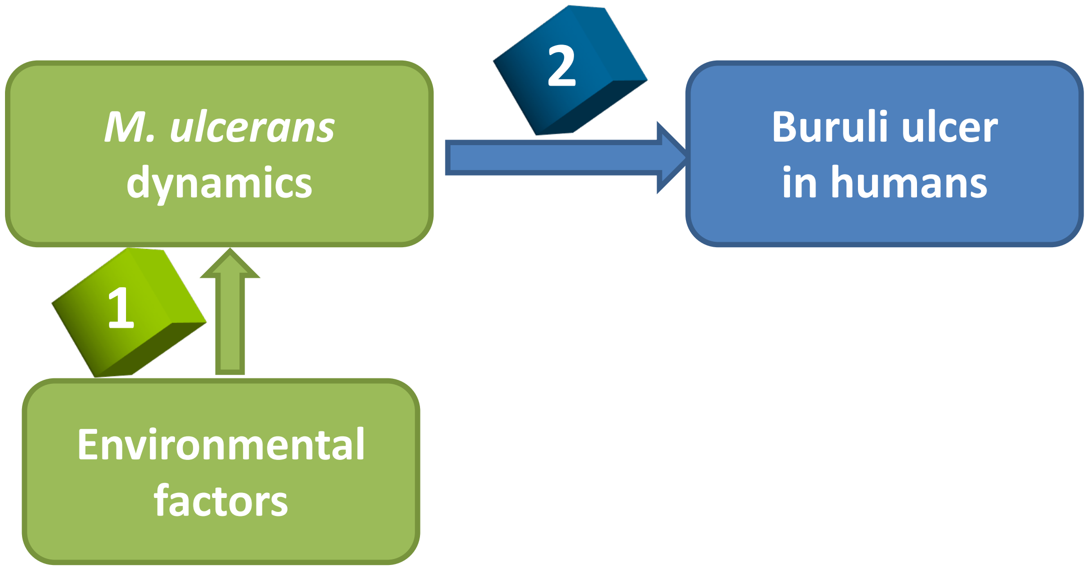
Buruli ulcer: a mysterious disease



iii Objectives of the project

General objective

To gain insights on the ecological determinants 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

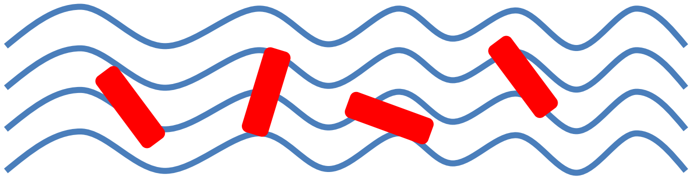
What do I need to characterize?

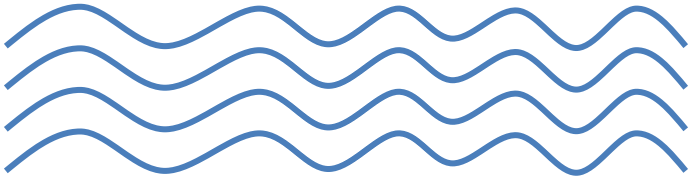
Spatial and/or temporal dynamics?

Relationships between parameters or systems?

DATA COLLECTION & DESCRIPTIVE ANALYSES

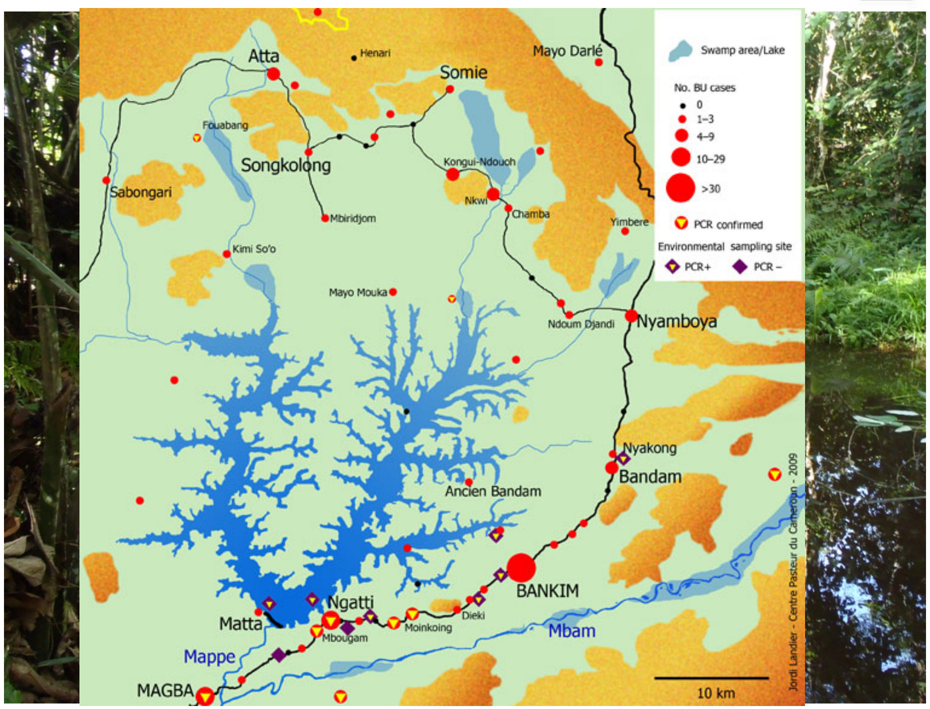
1 Introduction





1 Regions of study

Akonolinga	Bankim
• Landscape: Tropical rainforest • Historically endemic area (>40 years)	• Landscape: Savannah-Forest • New endemic area (10 years)



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

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

Characterization of MU in the environment

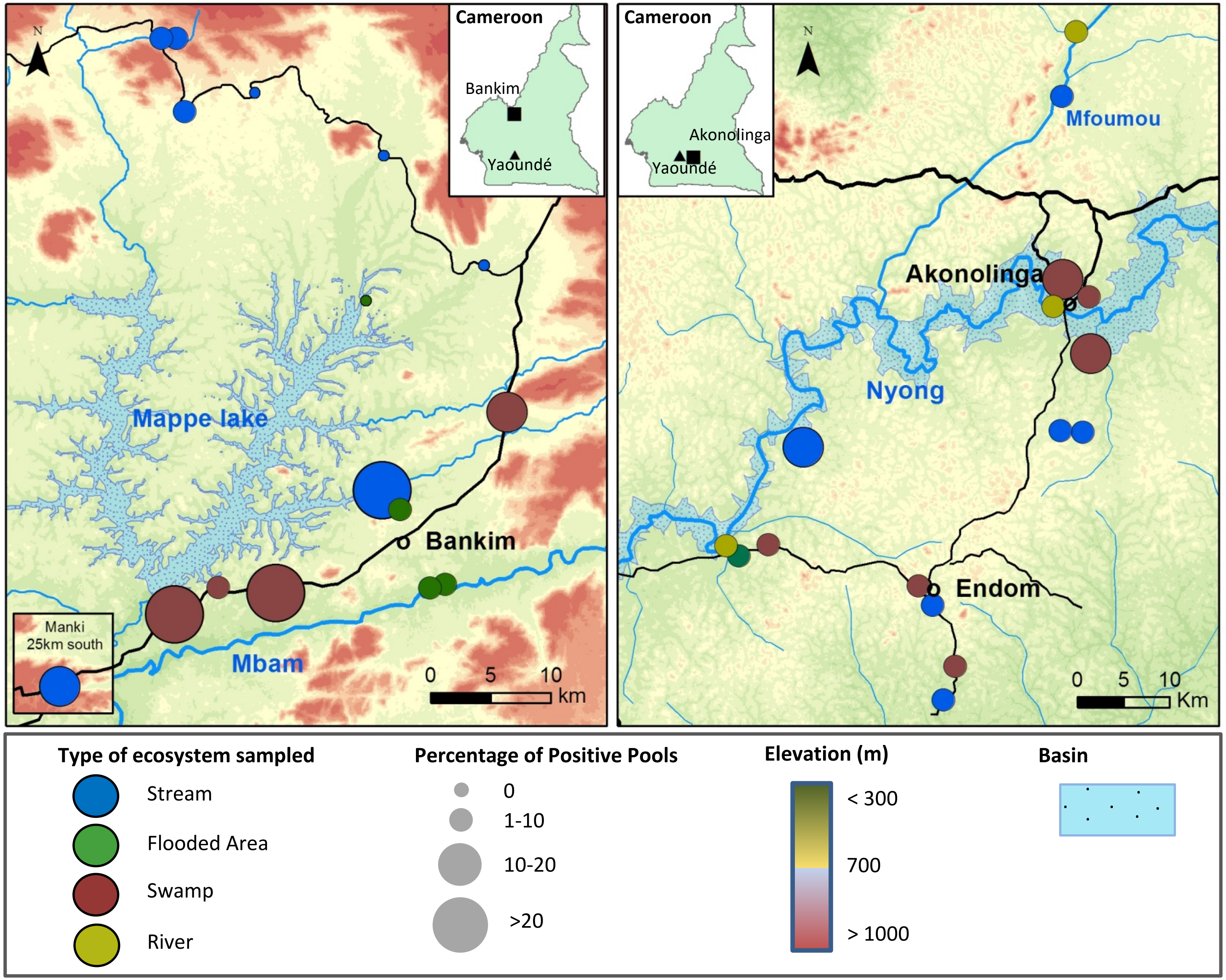
1. Fieldwork: Environmental sampling

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

3. Laboratory (Angers): DNA extraction & Amplification

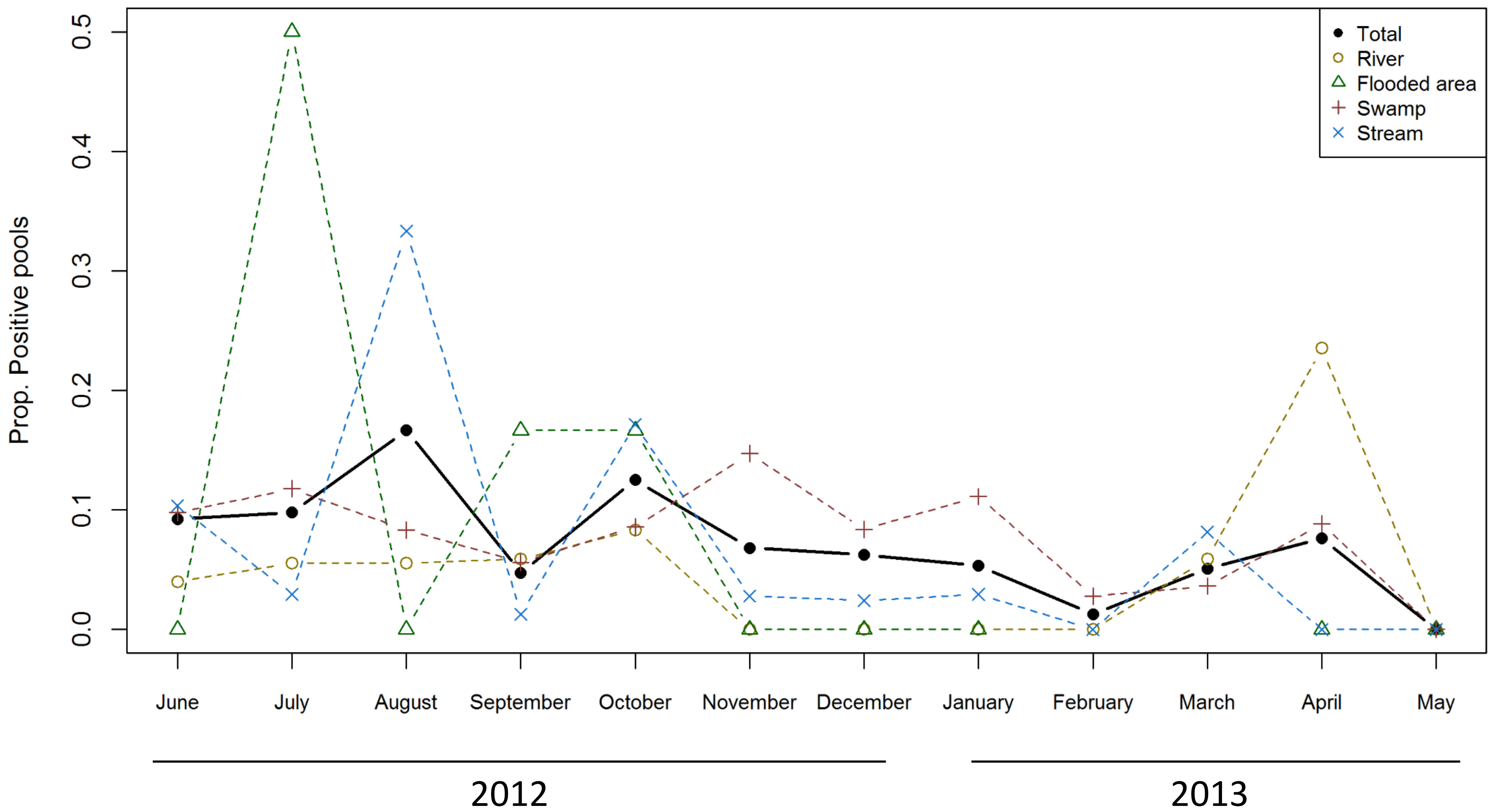
Characterization of MU in the environment

1 *M. ulcerans* geographical distribution



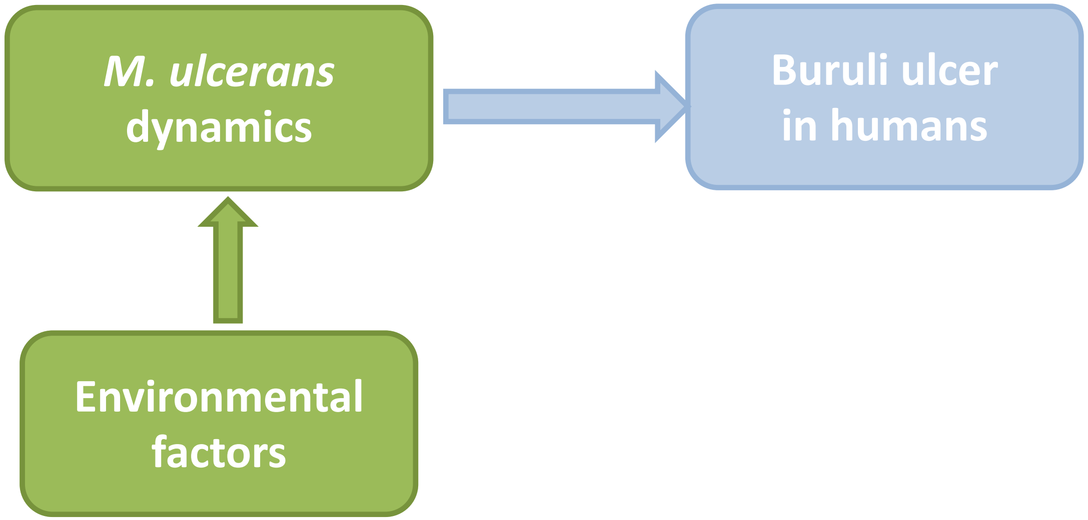
Garchitorena *et al.* (2014, *PloS NTDs*)

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



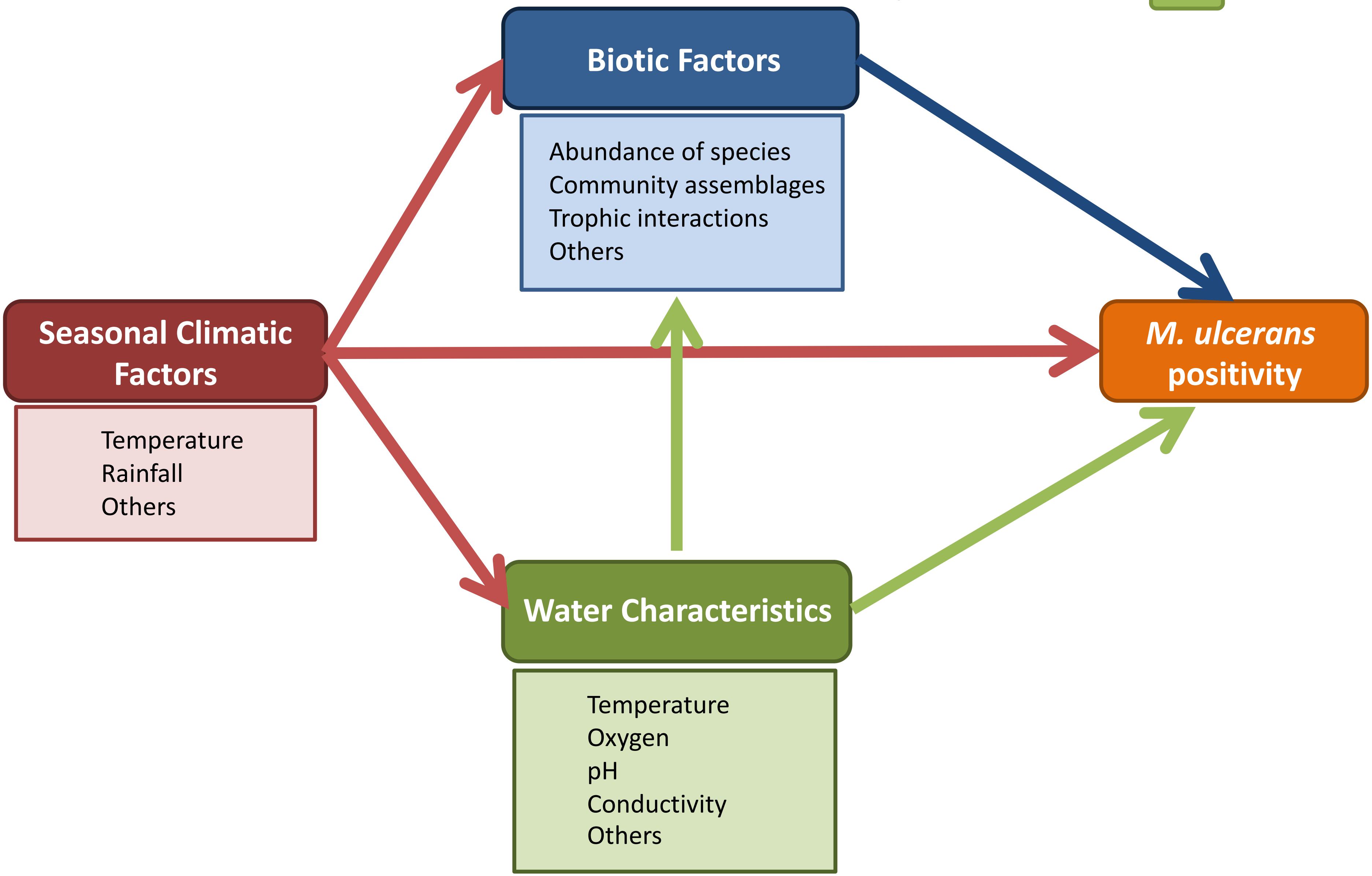
Garchitorena *et al.* (2014, *PloS NTDs*)

What type of modeling is necessary to answer my question?



STATISTICAL ANALYSES TO UNDERSTAND M. ULCERANS ECOLOGY

2 Environmental drivers of *M. ulcerans*



2 Methodology: Multi-model approach

Model Definition

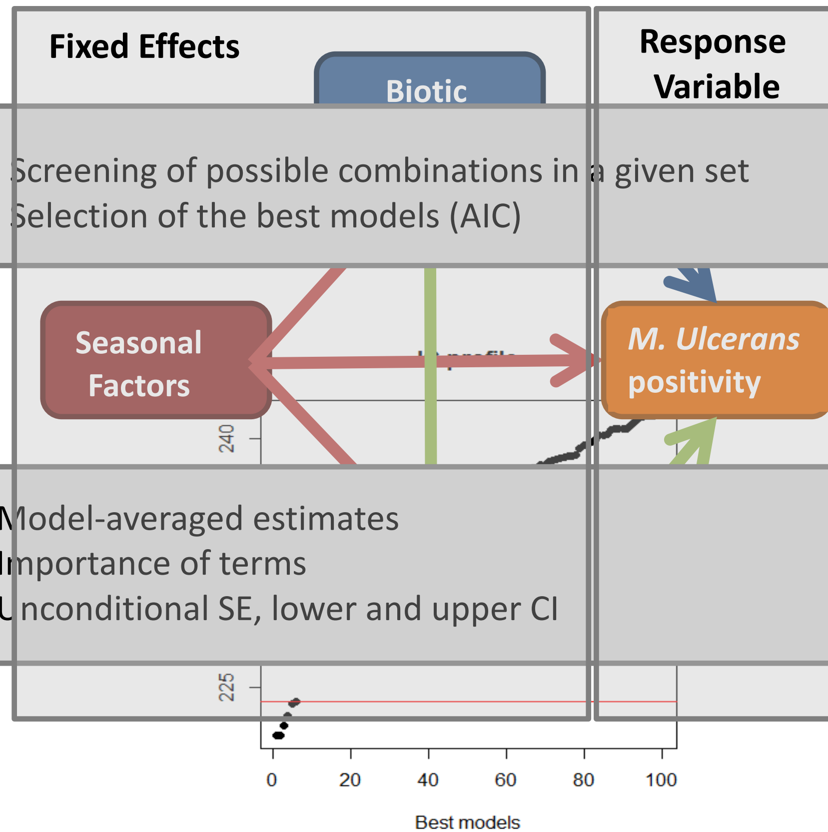
- Generalized linear mixed model (binomial)
- **Random effect**: Sample site

Multi-model Selection

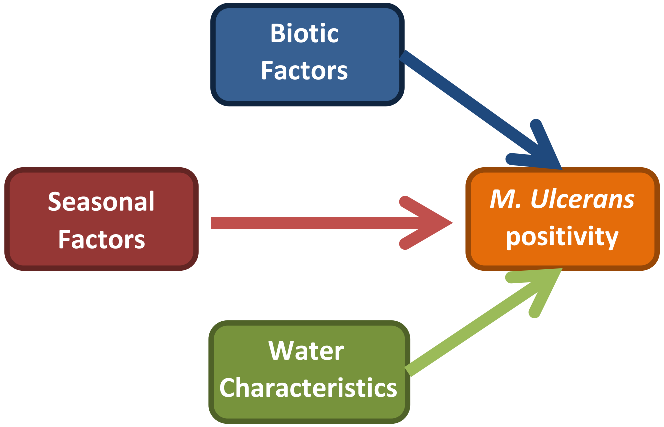
- Screening of possible combinations in a given set
- Selection of the best models (AIC)

Multi-model Inference

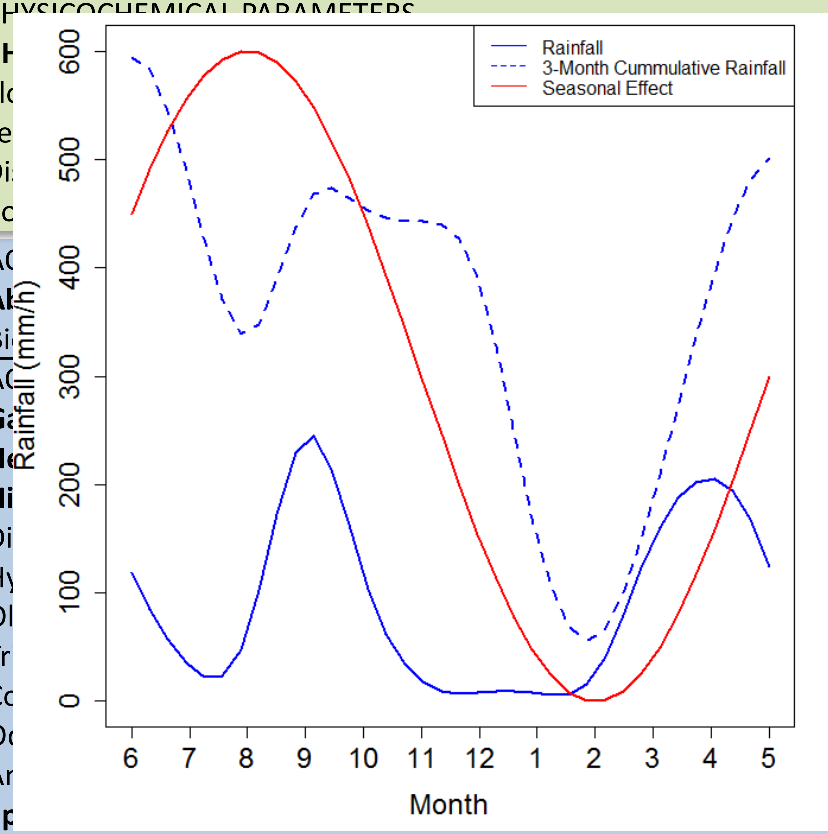
- Model-averaged estimates
- Importance of terms
- Unconditional SE, lower and upper CI



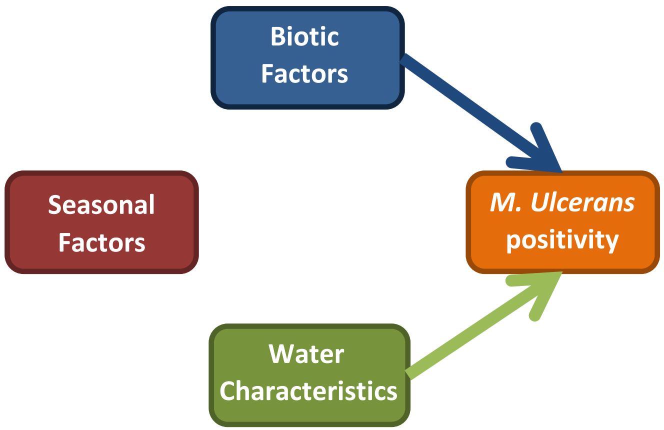
2 Environmental drivers of *M. ulcerans:* Akonolinga



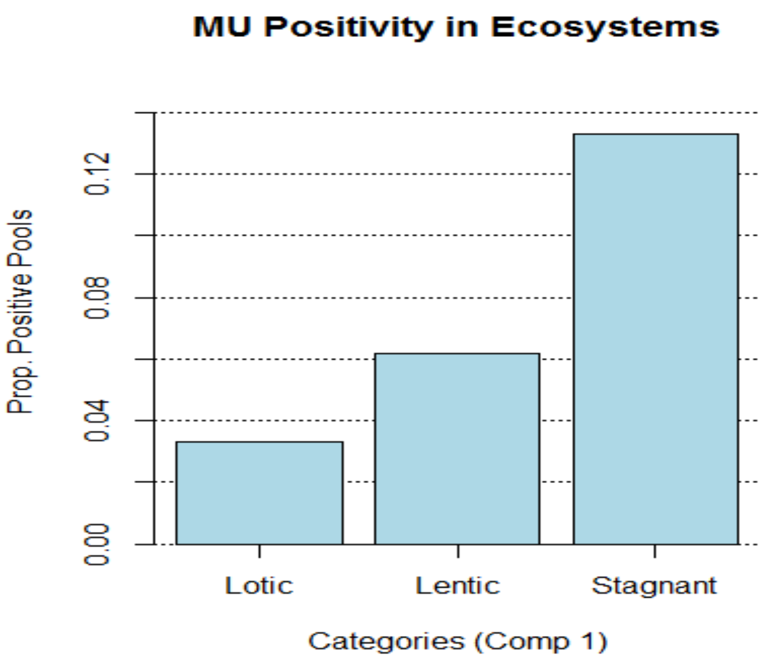
Variable	Avg.beta	Lower.CL	Upper.CL	Relative Importance
(Intercept)	**-13,66**	**-22,50**	**-4,82**	**1**
SEASONALITY				
Sin(2pi*Mois/12)	**0,35**	**0,02**	**0,69**	**1**
Sin(2pi*Mois/4)				
Cos(2pi*Mois/12)				
Cos(2pi*Mois/4)				
PHYSICOCHEMICAL PARAMETERS				
pH				
Fl				
Te				
Di				
Co				
AC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

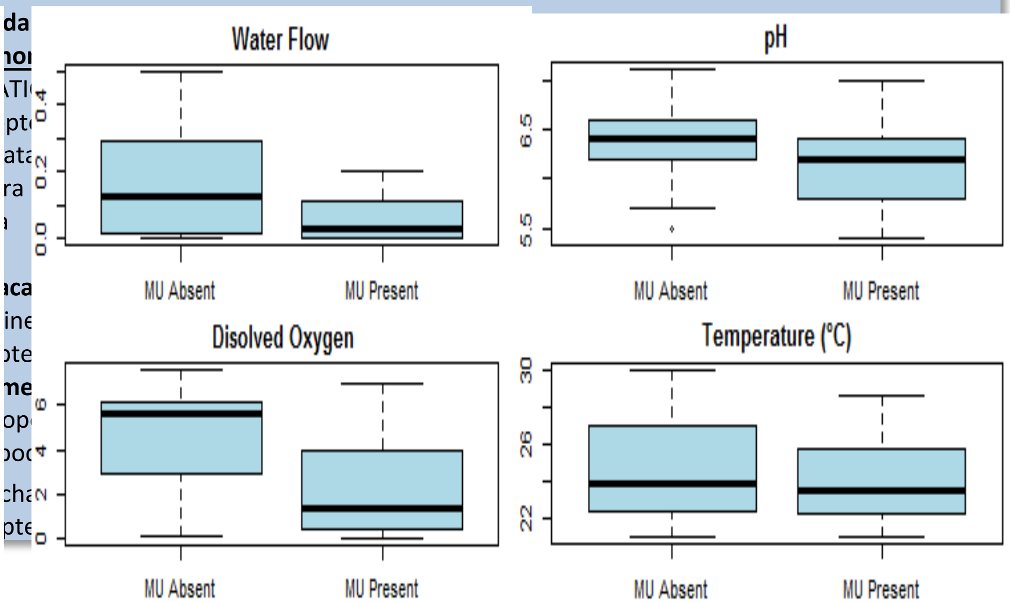


Environmental drivers of *M. ulcerans:* Bankim

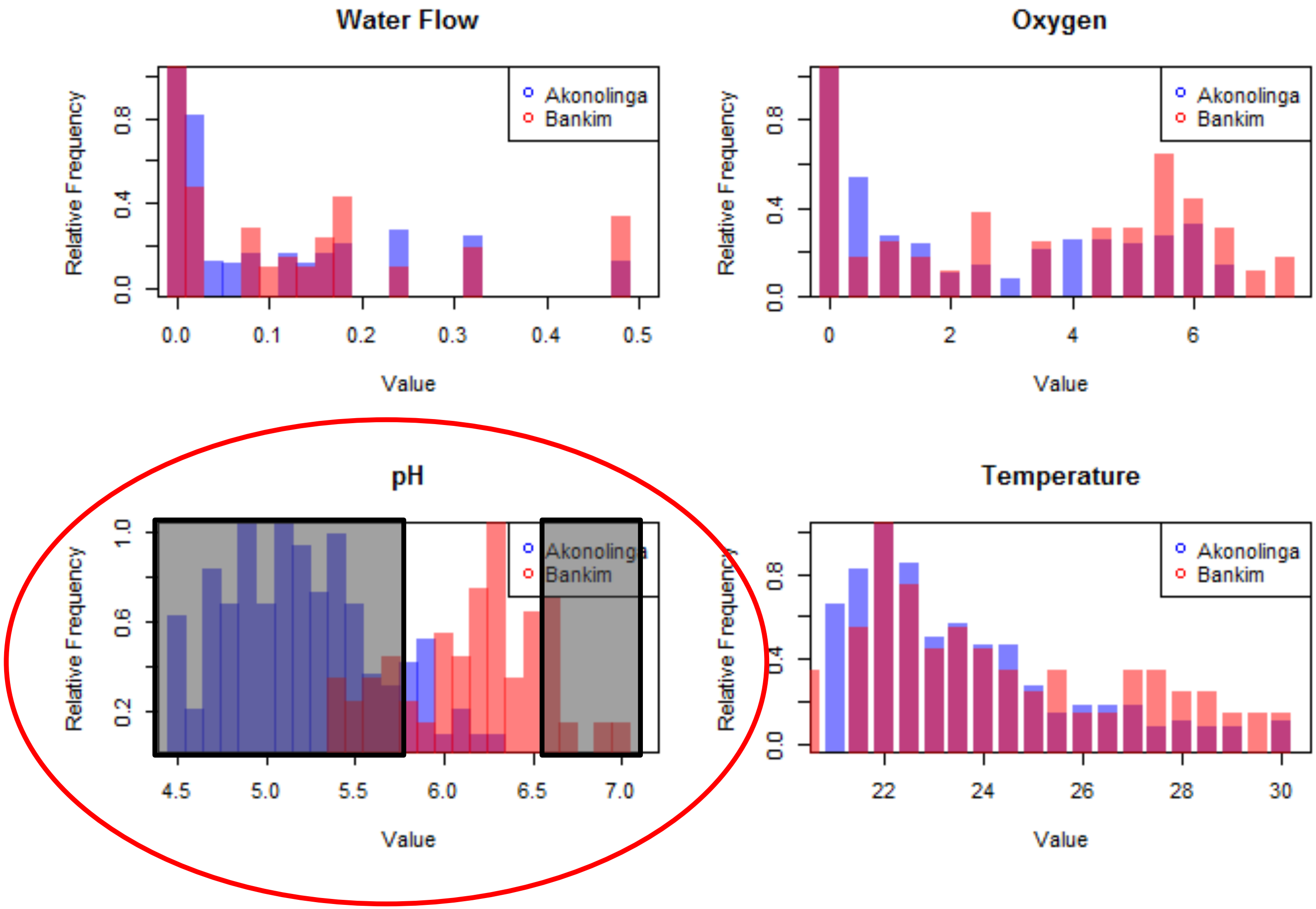


Variable	Avg.beta	Lower.CL	Upper.CL	Relative.Importance
(Intercept)	**-10,13**	**-18,94**	**-1,32**	**1**
PHYSICO-CHEMICAL PARAMETERS				
Water Flow (lentic)	**-1,91**	**-3,25**	**-0,57**	**1**
Water Flow (lotic)	**-2,86**	**-4,38**	**-1,33**	**1**
pH	-5,52	-15,64	4,61	0,02
Temperature				
Dissolved 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				





Why the two regions are so different?

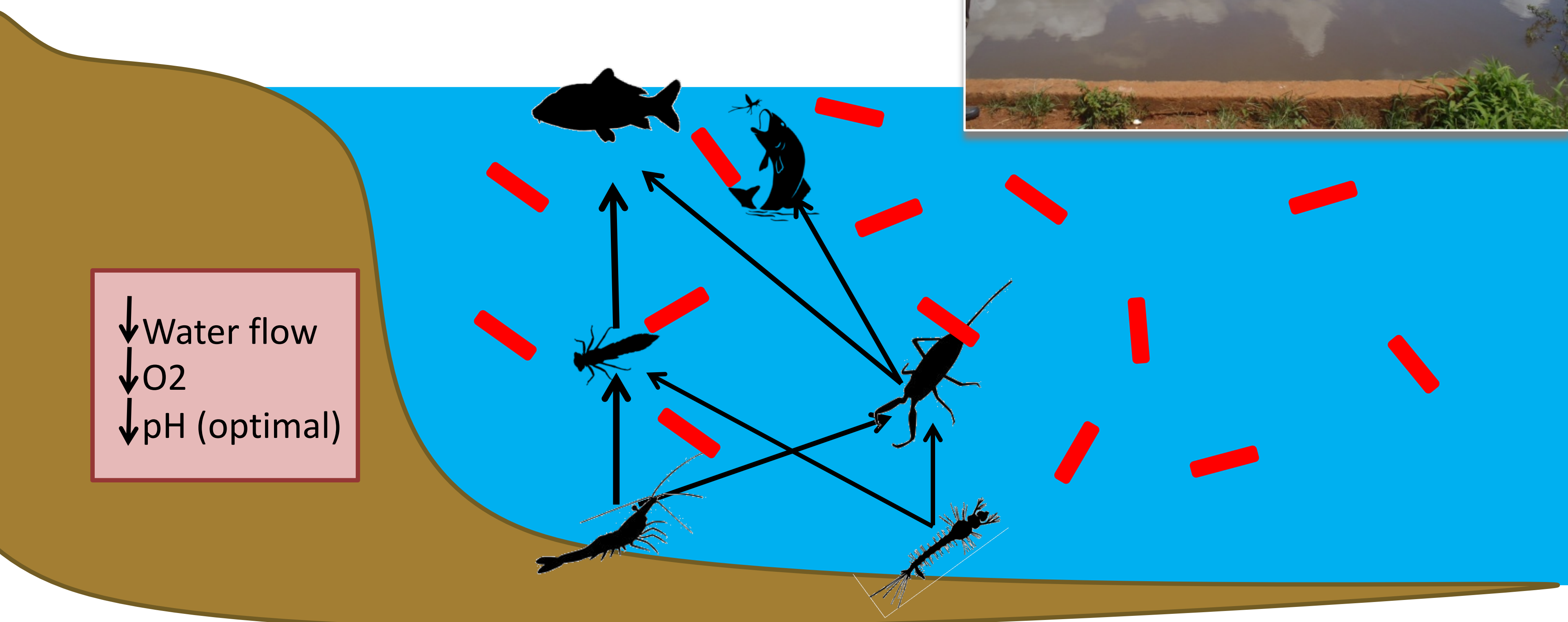


Optimal *pH* for *MU* [5.8-6.5]

2 Our theory

Scenario 1: Favourable physico-chemical conditions

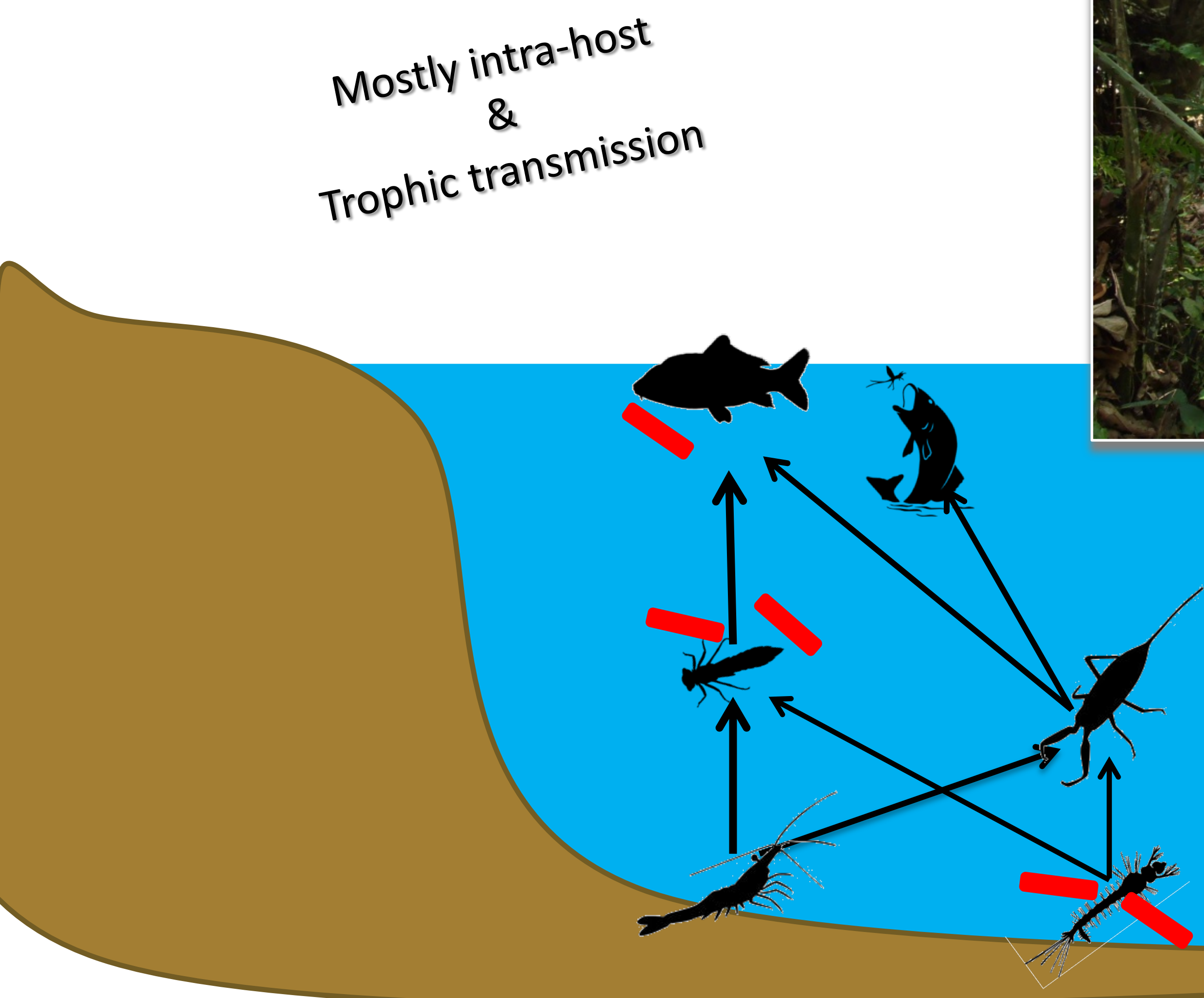
Free living stages
&
Environmental transmission to aquatic organisms



Environmental drivers of MU

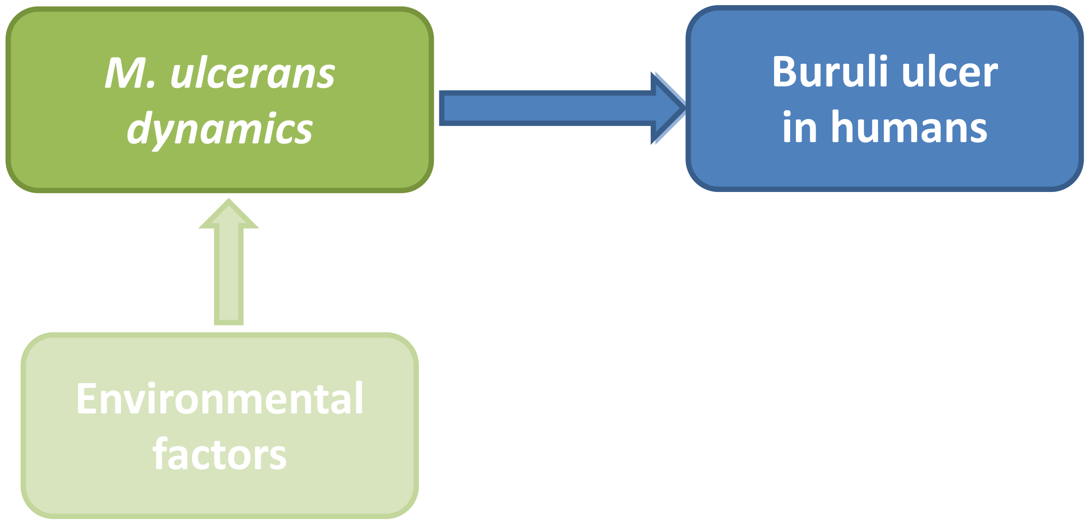
2 Our theory

Scenario 2: Adverse physico-chemical conditions

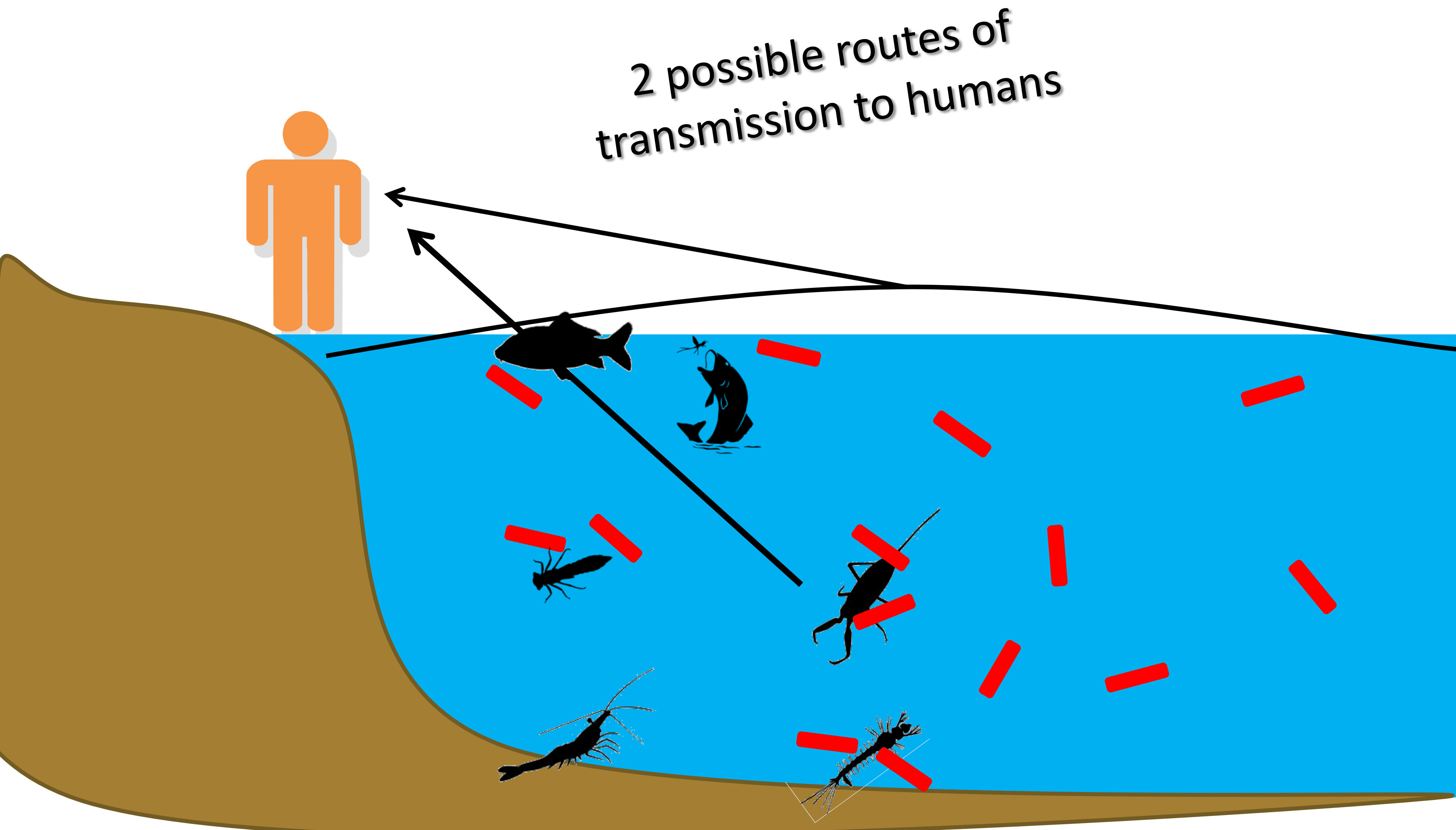


Environmental drivers of MU

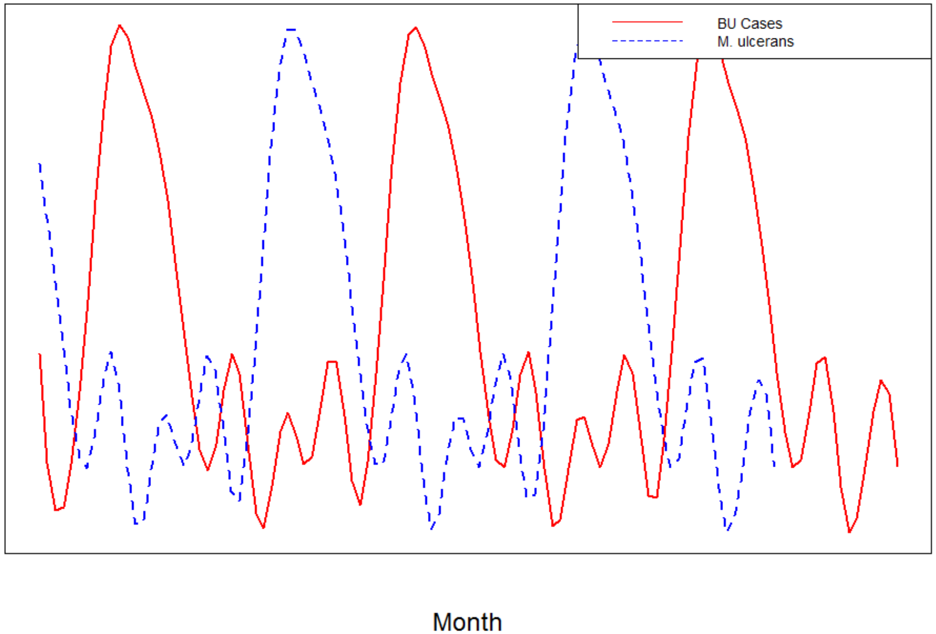
What type of modeling is necessary to answer my question?



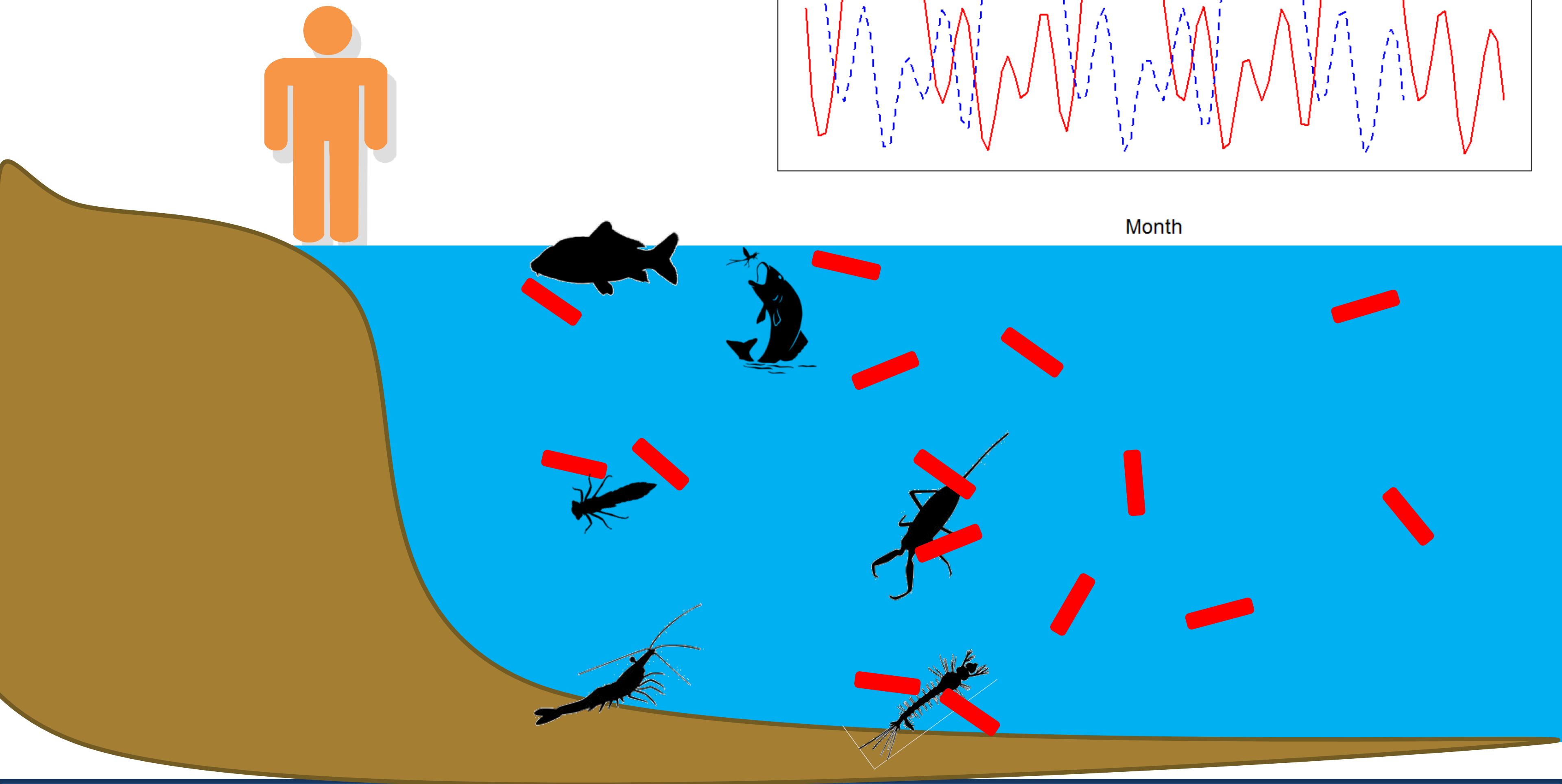
MATHEMATICAL MODELING TO UNDERSTAND BU TRANSMISSION


2 possible routes of transmission to humans

3 Introduction

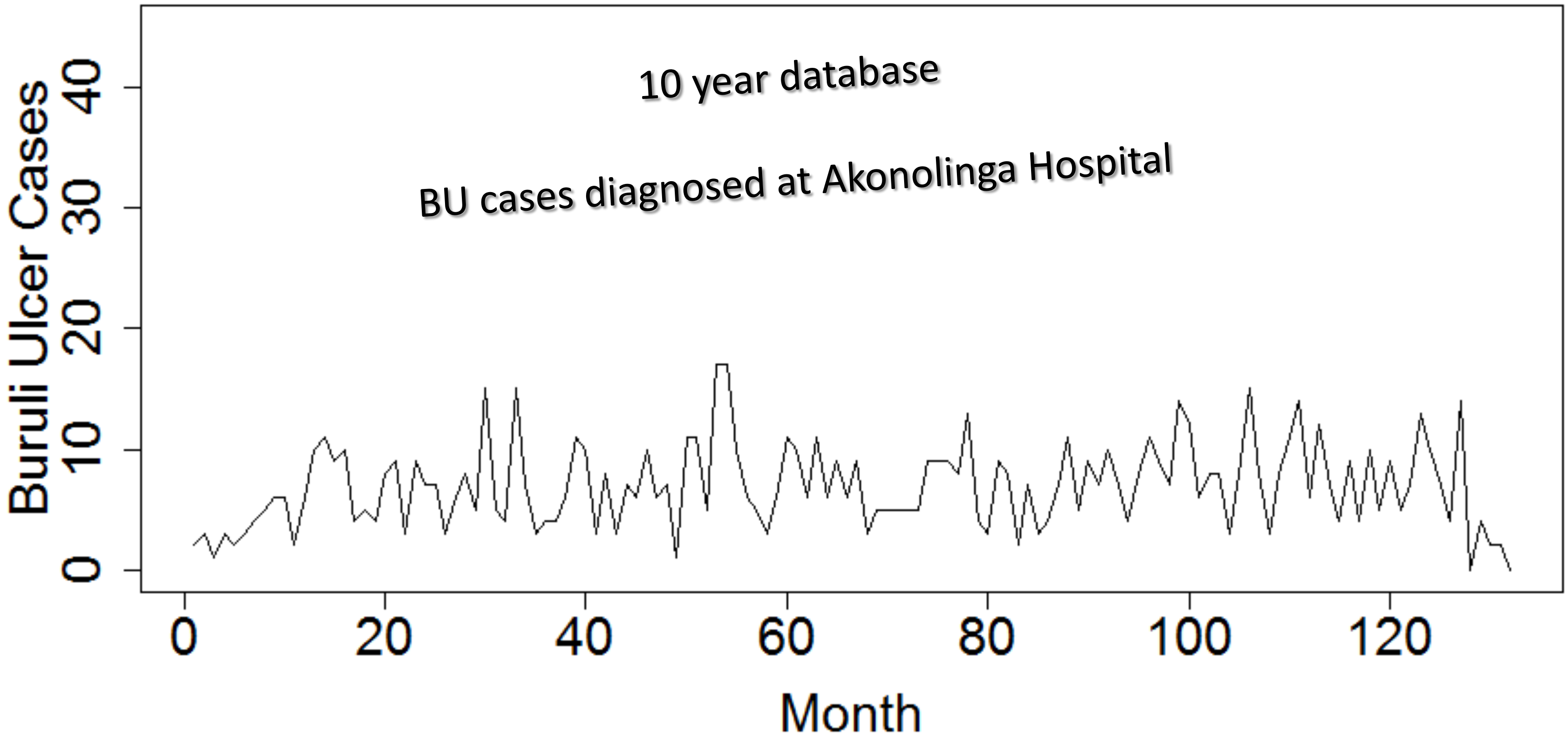


Dynamic model



Transmission of MU to humans

3 Temporal data



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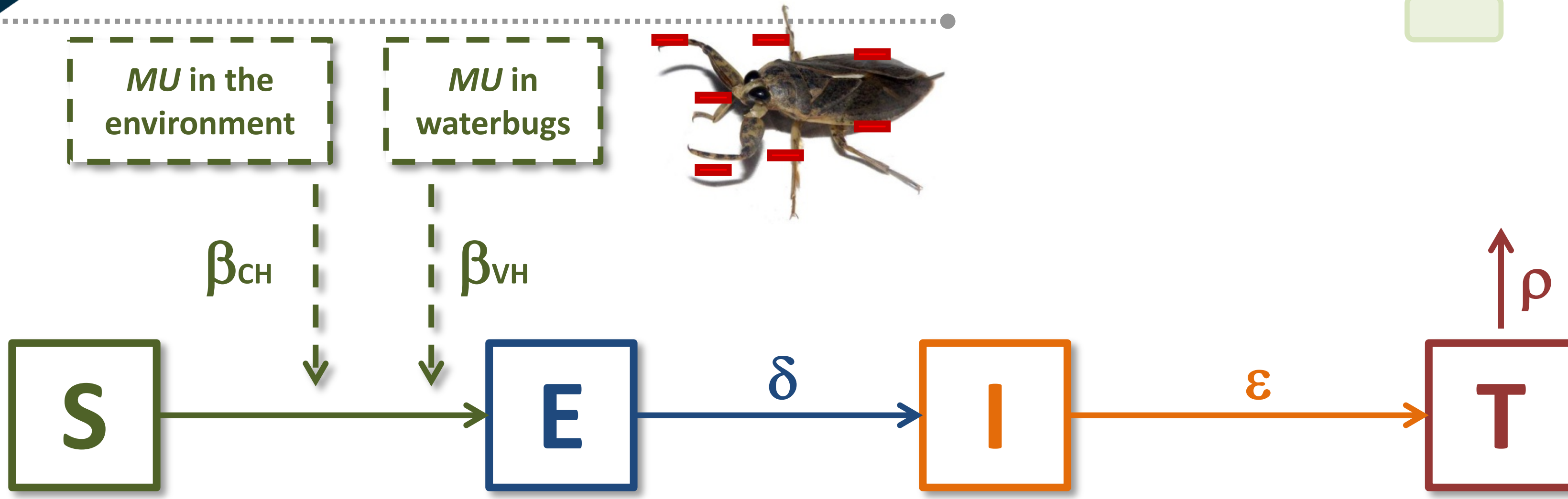
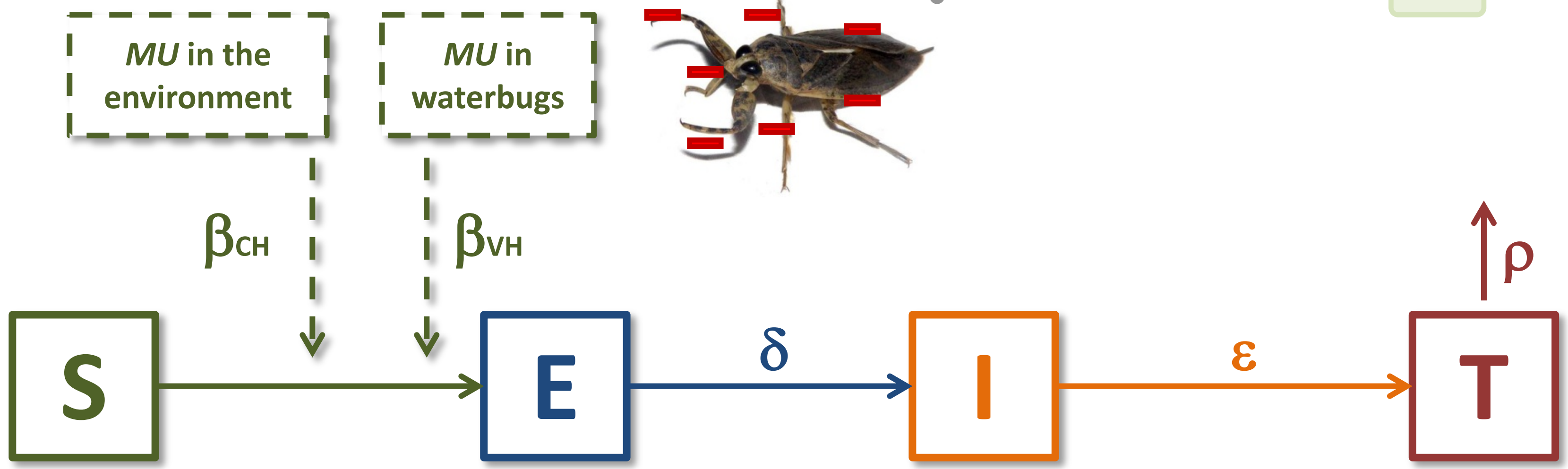
Mathematical model framework



Transmission of MU to humans

3

Mathematical model framework



Mathematical Model

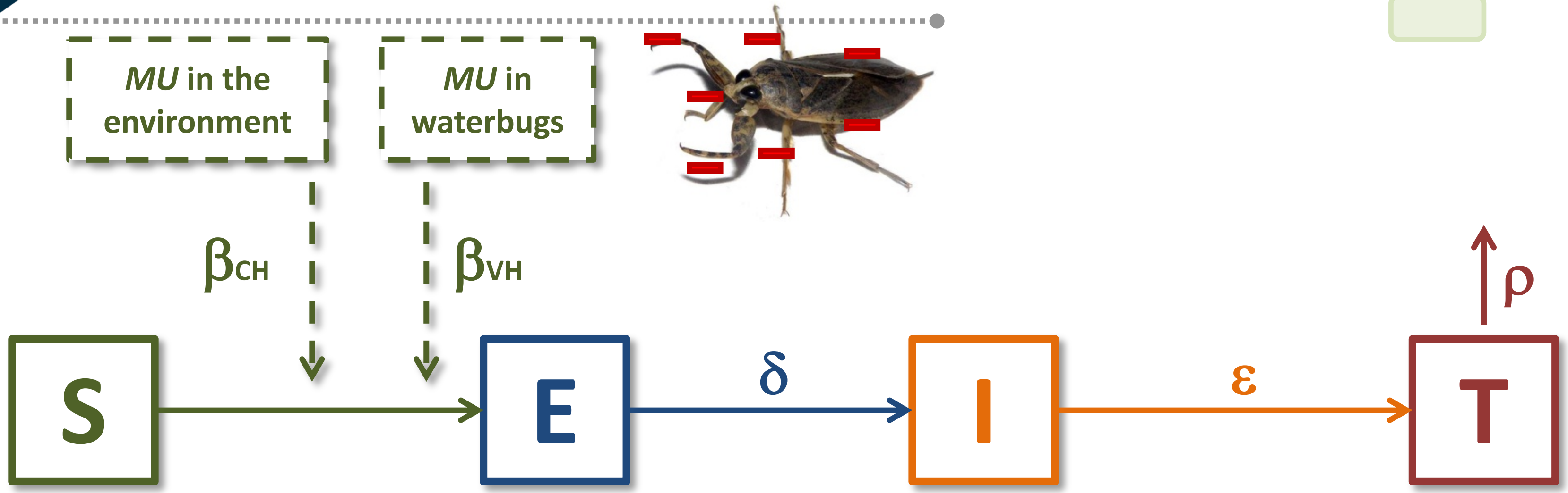
$$\frac{dS}{dt} = \mu N - \lambda_{CH}(Month_i)\,S - \lambda_{VH}(Month_i)\,S - \mu\,S$$

$$\frac{dE}{dt} = \lambda_{CH}(Month_i)\,S + \lambda_{CH}(Month_i)\,S - \sigma\,E - \mu\,E$$

$$\frac{dI}{dt} = \sigma\,E - \varepsilon\,I - \mu\,I$$

$$\frac{dT}{dt} = \varepsilon\,I - \gamma\,T - \mu\,T$$

3 Mathematical model framework

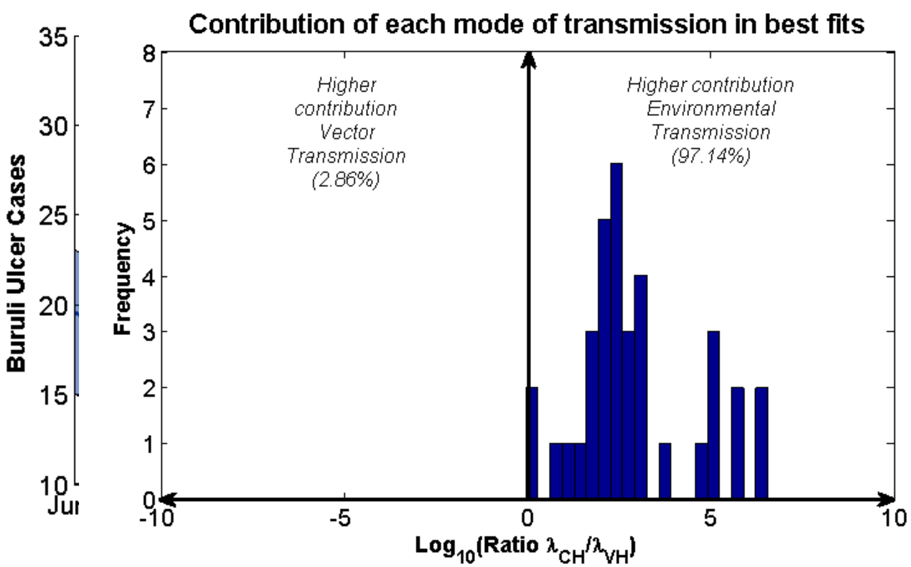


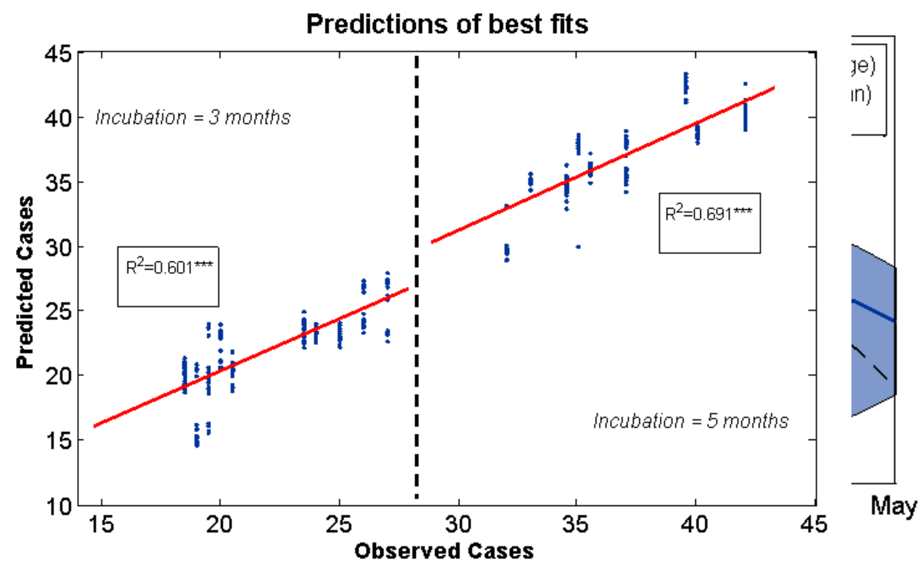
Model simulations to account for:

- A range of initial parameters
- Uncertainties in rates of incubation (δ) and seeking treatment (ε)
- Different proxies of waterbug tranmsission and environmental transmission
- Linear risks or thresholds in the relationship MU-BU

Comparison of model fit using AIC and selection of best performing (2 AIC)

Best temporal fit





Environmental transmission >>>> water bug transmission

MU environmental concentration as linear predictor of BU cases

AT THIS STAGE WE ARE ALMOST DONE…

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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E^2M^2 Workshop
Ranomafana, January 2019