

Health Analytics Workshop

MODELLING NEGLECTED TROPICAL DISEASES IN INDIA

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IIT Bombay, 30 Aug - 1 Sep 2023



Acknowledgements



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Who are we?



Luc E. Coffeng, MD PhD
Assistant Professor
PI for NTD Modelling Consortium
15 years of experience in NTD modelling



Ananthu James, PhD
Postdoctoral Researcher
Researcher for NTD Modelling Consortium
12 years of (quantitative) research experience
in life sciences and infectious diseases



Workshop objectives

- Foster links between the National Diseases Modelling Consortium and the NTD modelling consortium
- Build capacity within NDMC for NTD modelling, using VL as a case study





Workshop outline

Day 1

- Introduction to VL
- Formulate a model-answerable question
 - Translate to a conceptual model

Day 2

- Talks by guests and participants
- Hands-on: develop and apply your own compartmental model for VL

Day 3 (morning)

- Review of more complex models
- Talks by participants





Potential workshop outputs

- Paper on workshop process and lessons learnt regarding capacity building
- Paper on model-answerable research question (and the answer)

(These are to be completed after the workshop)





Who are you?

- 20 participants, all with some quantitative and/or modelling background
 - 55% with at least a PhD in a quantitative field
 - 65% with prior experience in mathematical modelling
- Majority (65%) comfortable with R, and 30% used it for modelling
 - 5 have no experience with R, but do know Python, MatLab, or C/C++
- 85% familiar with infectious diseases, 30% with NTDs, and 15% with VL
- Strong motivation to apply workshop teachings immediately



DAY 1



Erasmus MC
University Medical Center Rotterdam

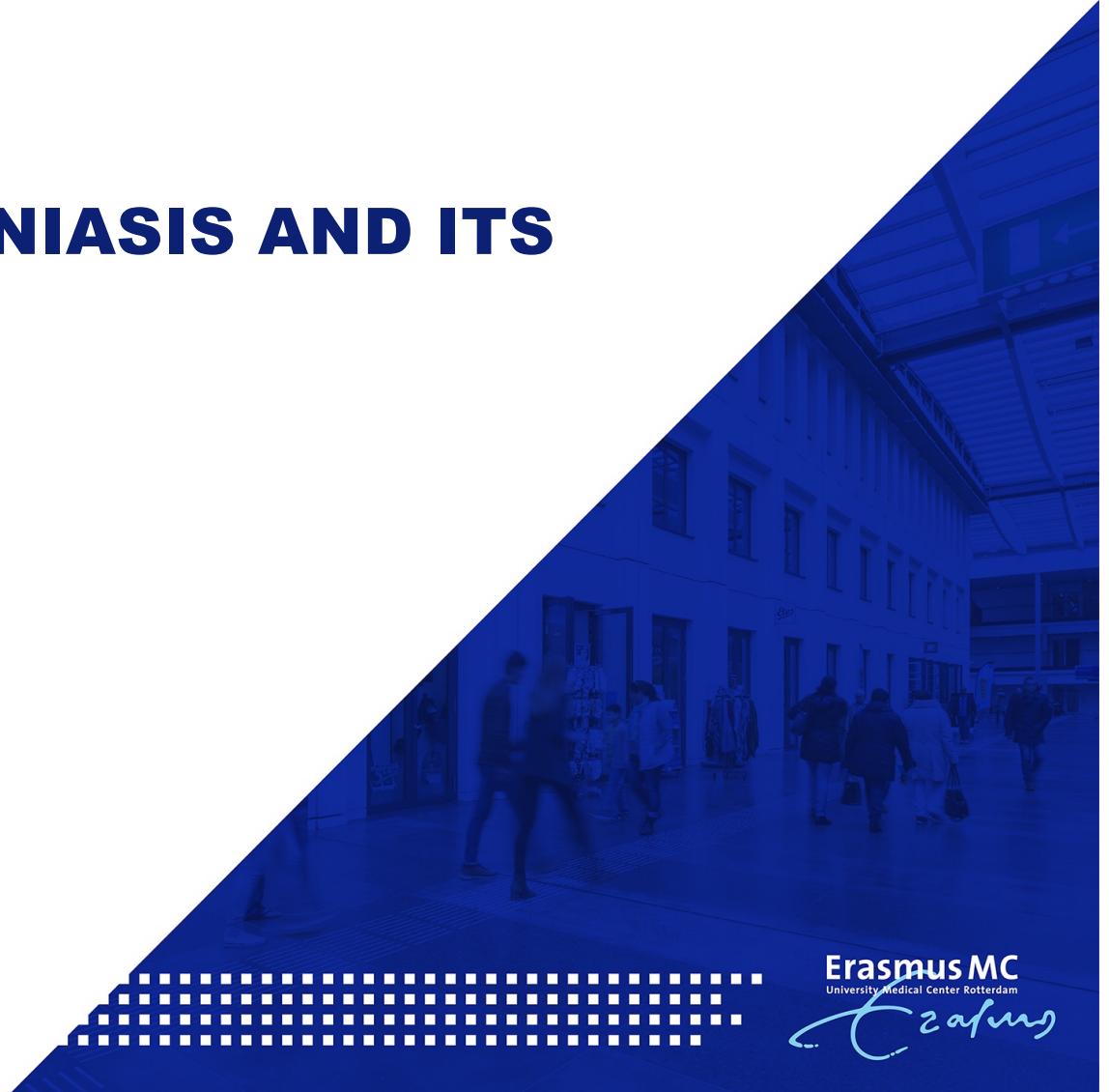



Day 1

9:45 am	General introduction + Background to the VL elimination program in India
10:45 am	Tea break
11:00 am	Break-out session: formulating a model-answerable question
11:15 am	Developing stochastic compartmental models
12:15 pm	Break-out session
12:45 pm	Lunch
2:00 pm	Interactive session based on morning break-outs
3:30 pm	Tea break
3:45 pm	Data needs and available data
5:00 pm	Close

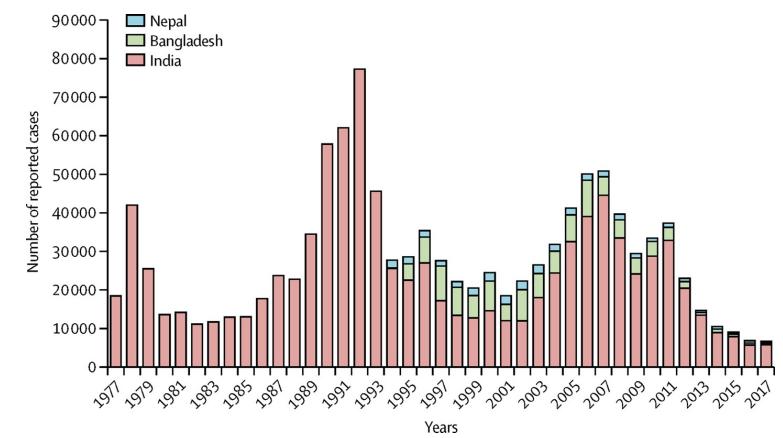
9:45 – 10:45 am

VISCERAL LEISHMANIASIS AND ITS CONTROL IN INDIA



Visceral leishmaniasis (VL)

- Protozoan blood parasite
 - In South Asia: *Leishmania donovani*
- Transmitted by sandfly vector
 - In South Asia: *Phlebotomus spp.*
- VL is the symptomatic stage of infection
 - Minority of infections become symptomatic (<5%)
 - Symptoms lead to death unless treated
- Control relies on prompt case detection/treatment and vector control



Burza et al. 2018 Lancet

Erasmus MC


A spatio-temporal approach to short-term prediction of visceral leishmaniasis diagnoses in India

Emily S. Nightingale, Lloyd A. C. Chapman, Sridhar Srikanth, Swaminathan Subramanian, Purushothaman Jambulingam, Johannes Bracher, Mary M. Cameron, Graham F. Medley

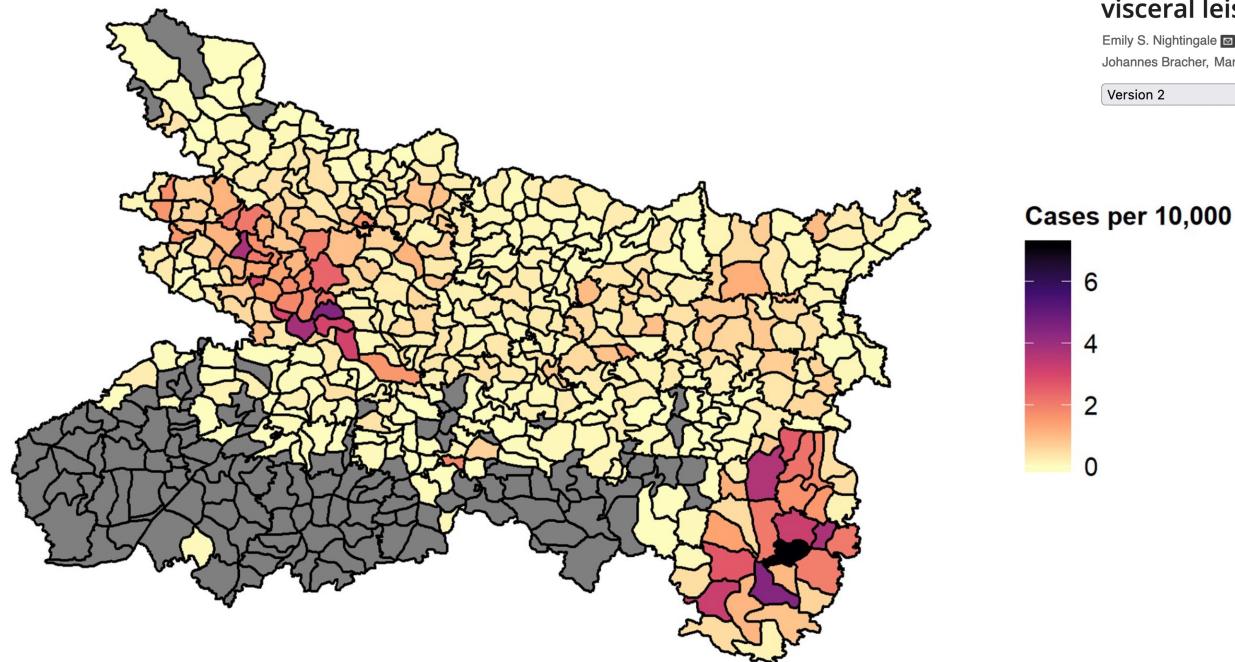
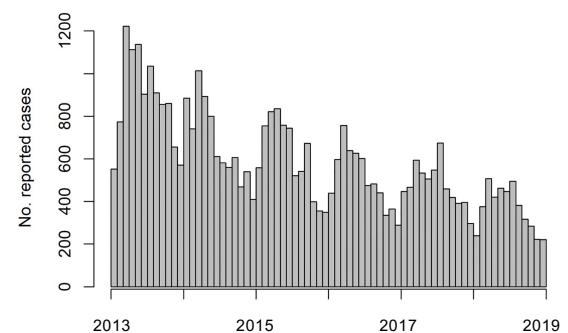
Version 2 Published: July 9, 2020 • <https://doi.org/10.1371/journal.pntd.0008422>

Fig 1. Estimated incidence per 10,000 population per block in 2018, for Bihar and the four endemic districts of Jharkhand (Dumka, Godda, Sahibganj and Pakur). Incidence is estimated according to reported cases in KA-MIS with diagnosis date in between 01/01/2018 and 31/12/2018 and block populations projected from the 2011 census according to decadal, block-level growth rates [9]. Black lines indicate block boundaries. The affected blocks of Jharkhand on average have much higher incidence than Bihar and can be seen in the bottom right of the map. Blocks marked grey had no reported cases during the study period.



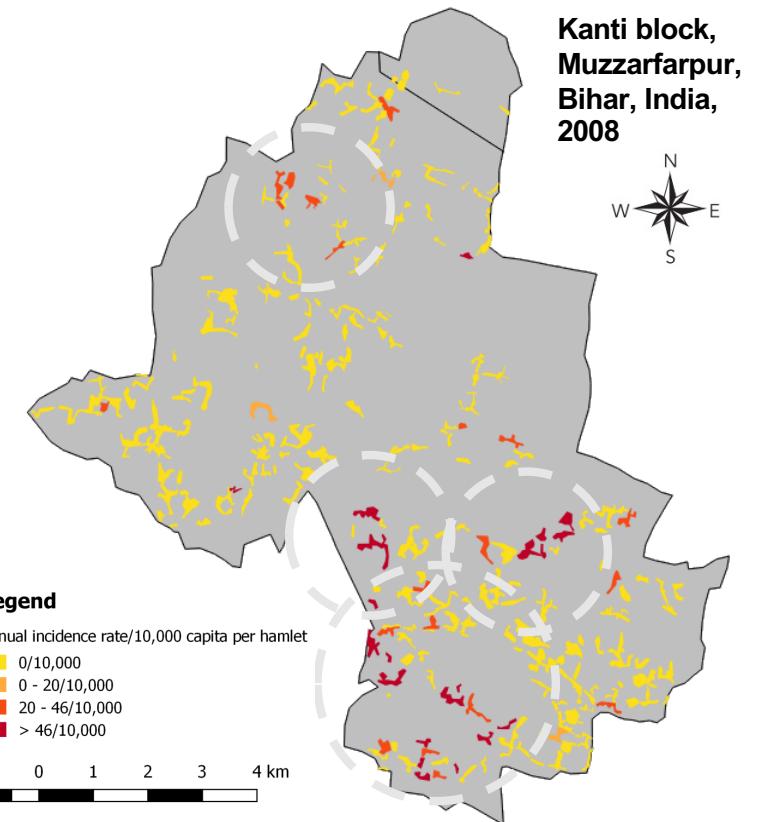
Wandering epidemic

Local VL outbreaks that last about 2 to 3 years

Majority of cases ($\frac{2}{3}$ to $\frac{3}{4}$) occur in recently affected villages

Outbreaks seem to wander from village to village

- Some villages are never affected (in recorded history)
- Prevalence and intensity of antibody titres probably indicate how recently a village was affected



Bulstra et al. 2018 PLoS Negl Trop Dis

Clinical aspects of VL

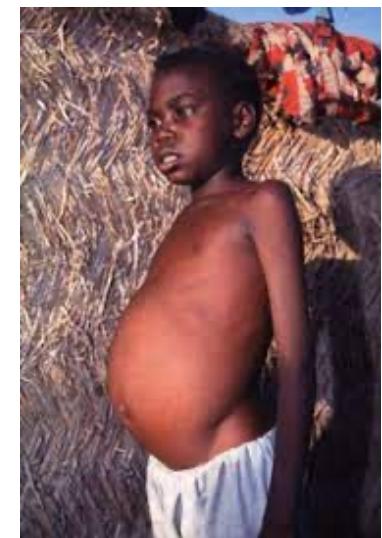
Symptoms develop about 7 months after infection by the sandfly (on average)

- Each year, Incidence of reported VL cases peaks around March-April



Diagnosis

- Fever (>2 weeks required for diagnosis)
- Detectable antibodies
 - In clinical settings, rK39 test is used (low specificity if fever <2 weeks)
 - In study settings, DAT (direct agglutination test) is also often used
 - High antibody titres in asymptomatic cases are a strong predictor of developing VL
 - Individual antibody positivity can fluctuate over time (months to years)
- Enlarged liver and spleen
- Parasites in spleen or bone marrow sample



Treatment of VL

- Intravenous drugs
- Requires diagnosis and hospital admission

The parasite that persists

- 5-20% of treated cases develop post-kala-azar dermal leishmaniasis (PKDL)
 - Several forms (e.g., macular and nodular)
 - Chronic condition (order of years)
 - Most cases do not seek diagnosis / treatment
 - Equally infectious towards sandflies as VL
- Immuno-compromising conditions (e.g., untreated HIV infection) may lead to re-activation of previously treated VL
- Antibodies fluctuate over the years (KALANET study)
 - Hypothesis: occasional contact of host immune system with resident parasites and/or re-exposure to infected sandfly



Who is infecting sandflies?

Sandfly feeding experiments

- Assess the infectivity of different stage of human infection towards sandflies
 - Study in Bangladesh: Mondal *et al.* (2019) Clin Infect Dis
 - Study in India: Singh *et al.* (2021) Lancet Microbe



PKDL

- Half (Bangladesh) or equally likely (India) to infect sandflies, relative to VL
- Nodular PDKL is more infective than macular PKDL

Asymptomatic infections

- 0% (in a sample of 122 individuals with detectable antibodies)

Sandfly biology

- Short fly lifespan (~14 days on average)
- ~5 days until infected flies become infectious towards humans
- Extremely low infection prevalence in sandflies (<<1%– 5%)
- Unlikely to fly long distances → humans primarily responsible for geographical spread
- Seasonal abundance with peak in July-August, almost absent during winter



Unknown about sandflies

- Where do they breed?
- Where do they bite / transmit? Indoors or outdoors?
 - Not uncommon for people to sleep outdoors during hot season
- Where / how do they survive winter?

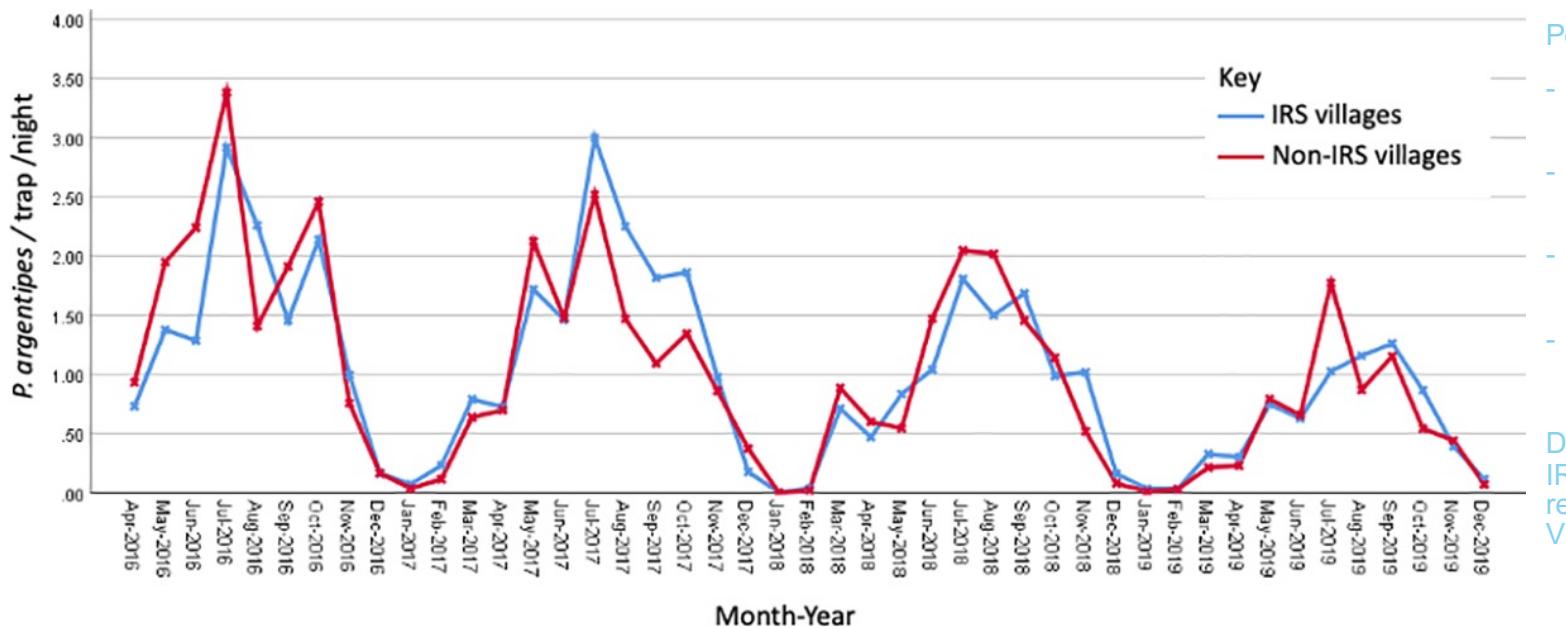
Vector control

- Indoor residual spraying (IRS) with synthetic pyrethroids
 - Expensive and quite challenging (e.g., access to cleared-out homes, highly variable insecticide concentrations on walls)
 - Historically, strong impact of DDT spraying (malaria control) on VL case incidence, but full-blown resistance to DDT by now
- Unknown how IRS decreases overall sandfly abundance
 - Larvicidal effect (i.e., fewer flies “born”)? ([linear effect on transmission](#))
 - Decreased adult sandfly lifespan? ([reduces transmission probability / fly](#))
 - Repel flies? ([quadratic effect on transmission](#))
- IRS implementation
 - Initiated at village-level when there has been a VL case
 - Applied twice per season (protects for ~3 months)
 - Stopped after 3 years of no VL cases

Insecticide-treated bed nets: no clear evidence for an effect



Secular trend in sandfly abundance



Potential contributors:

- Agricultural use of insecticides
- Changing housing conditions
- Climate change (probably not)
- ...

Difficult to interpret impact of IRS as this is implemented reactively in response to local VL case occurrence!!!

Deb et al. 2021 PLoS Negl Trop Dis

2030 Control targets for South Asia

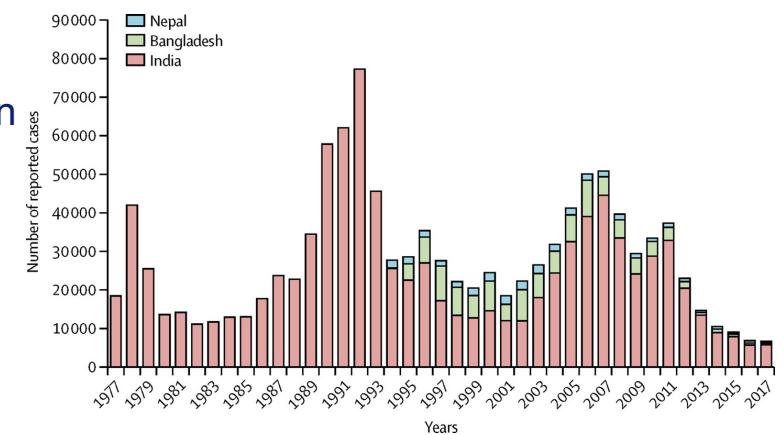
- ≤ 1 VL case / 10,000 / year at the block level
- ≤ 1 VL death / 10,000 / year at the block level
- Detect and treat PKDL

Challenge: incidence rates depend on detection effort

- Anecdotally, 50% of all cases used to die without detection (<2010)

15-year “cycles” in case numbers:

- My hypothesis: due to case detection efforts and spraying (including malaria control programs)
- Some others: due to biology and epidemiology of the disease (e.g., like measles)



Burza et al. 2018 Lancet

EXAMPLES OF QUESTIONS THAT MODELS HAVE TRIED TO ADDRESS (NON-EXHAUSTIVE)

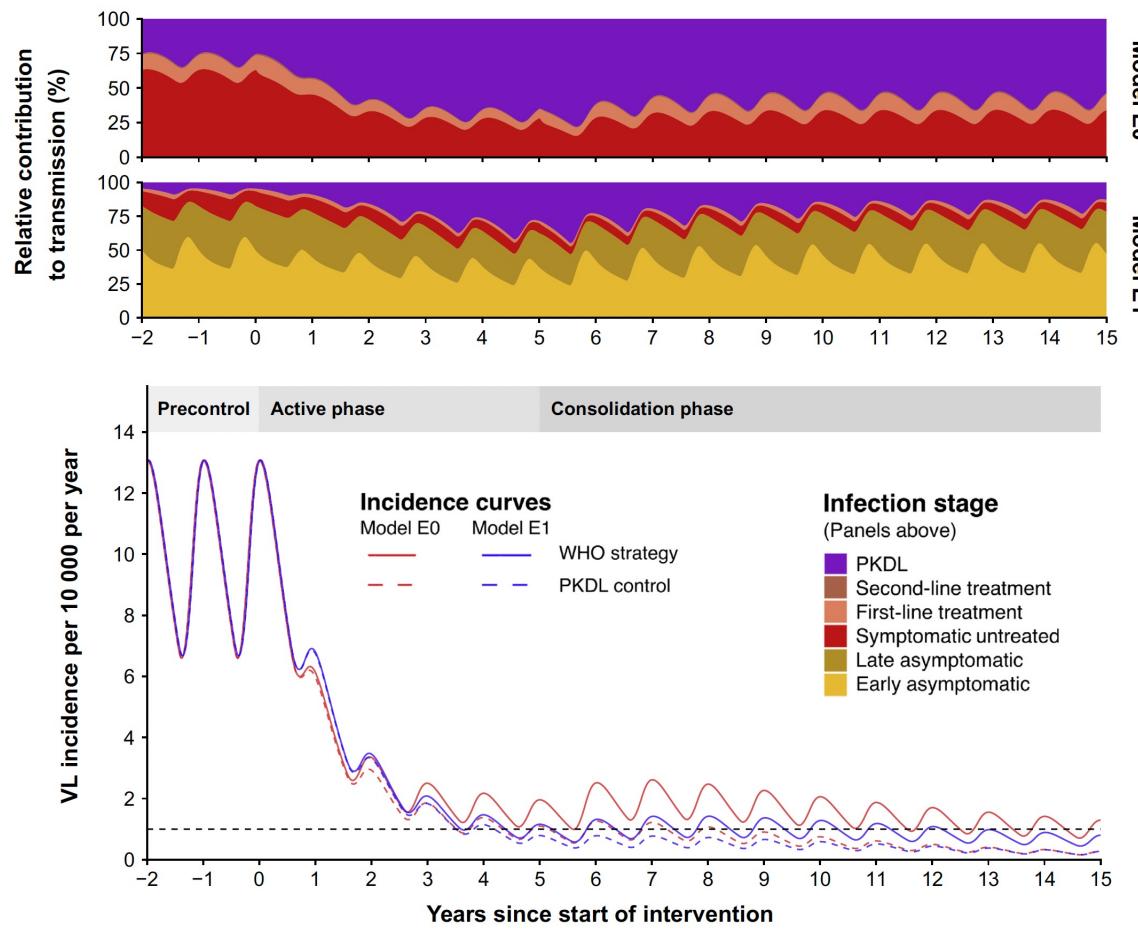




Example 1

- Is it important who transmits infection to sandflies?
 - What / who is mainly driving or sustaining transmission when nearing the control targets?
 - What can we do to push infection levels further down?





Post-Kala-Azar Dermal Leishmaniasis as a Reservoir for Visceral Leishmaniasis Transmission

Epke A. Le Rutte,^{1,2,3,*}
Eduard E. Zijlstra,⁴ and
Sake J. de Vlas¹



Trends in Parasitology, August 2019, Vol. 35, No. 8

- Deterministic model
- Seasonal transmission
- Detailed sub-model for clinical management
- Simulation of control measures as recommended by WHO (grey bar over graph)



Example 2

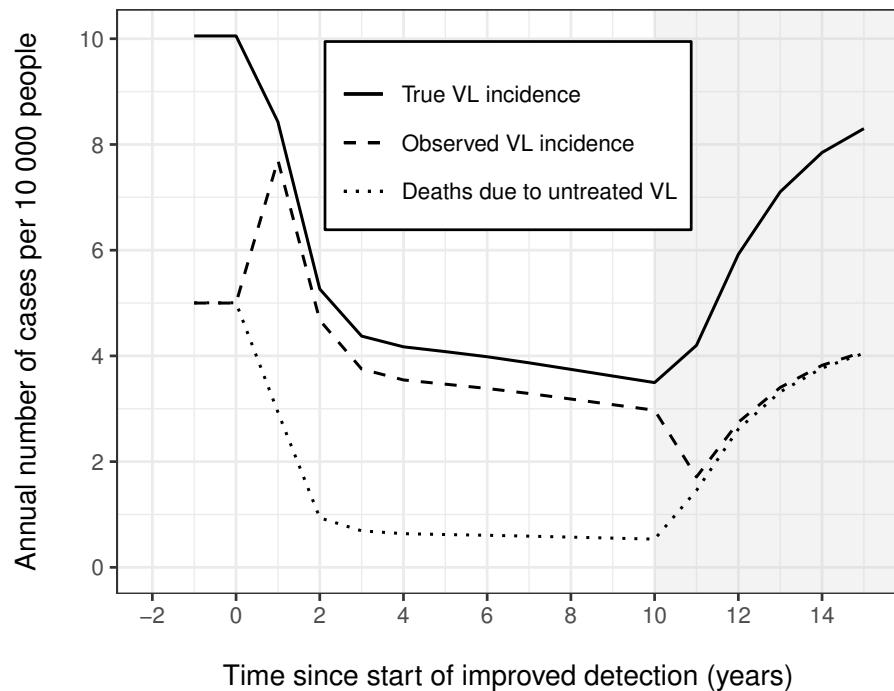
- How problematic is it that the control targets are specified in terms of something that depends how hard you look for cases?
 - What are potential markers of “sufficient” detection effort?



Impact of Changes in Detection Effort on Control of Visceral Leishmaniasis in the Indian Subcontinent

Luc E. Coffeng,^{1,2} Epke A. Le Rutte,^{1,2,3,a} Johanna Muñoz,^{1,a} Emily R. Adams,⁴ Joaquin M. Prada,⁵ Sake J. de Vlas,¹ and Graham F. Medley⁶

¹Department of Public Health, Erasmus MC, University Medical Center Rotterdam, Rotterdam, The Netherlands, ²Department of Epidemiology and Public Health, Swiss Tropical and Public Health Institute, Basel, Switzerland, ³University of Basel, Basel, Switzerland, ⁴Department of Tropical Disease Biology, Liverpool School of Tropical Medicine, Liverpool, United Kingdom, ⁵School of Veterinary Medicine, Faculty of Health and Medical Sciences, University of Surrey, Guildford, United Kingdom, and ⁶Centre for Mathematical Modelling of Infectious Disease and Department of Global Health and Development, London School of Hygiene and Tropical Medicine, London, United Kingdom



- Deterministic and stochastic model versions
- Detailed sub-model for case detect effort (which you will have as part of your template model later on)



Example 3

- How might we monitor VL transmission after achieving the control targets?
 - What can antibody surveys tell us?

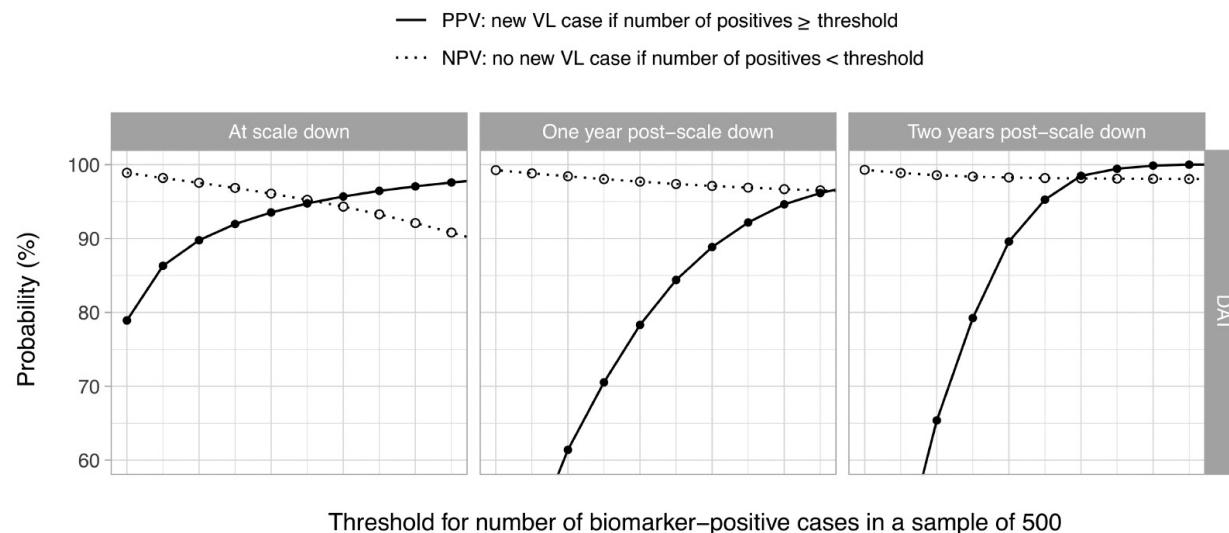


Antibody and Antigen Prevalence as Indicators of Ongoing Transmission or Elimination of Visceral Leishmaniasis: A Modeling Study

Luc E. Coffeng,^{1,2} Epke A. Le Rutte,^{1,2,3} Johanna Munoz,¹ Emily Adams,⁴ and Sake J. de Vlas¹

¹Department of Public Health, Erasmus MC, University Medical Center Rotterdam, Rotterdam, The Netherlands; ²Department of Epidemiology and Public Health, Swiss Tropical and Public Health Institute, Basel, Switzerland; ³University of Basel, Basel, Switzerland; and ⁴Department of Tropical Disease Biology, Liverpool School of Tropical Medicine, Liverpool, United Kingdom

- Stochastic model
- Database of many repeated simulations of local transmission
- Analysis of predictive value of prevalence of different markers for recurrence of VL cases in a simulation



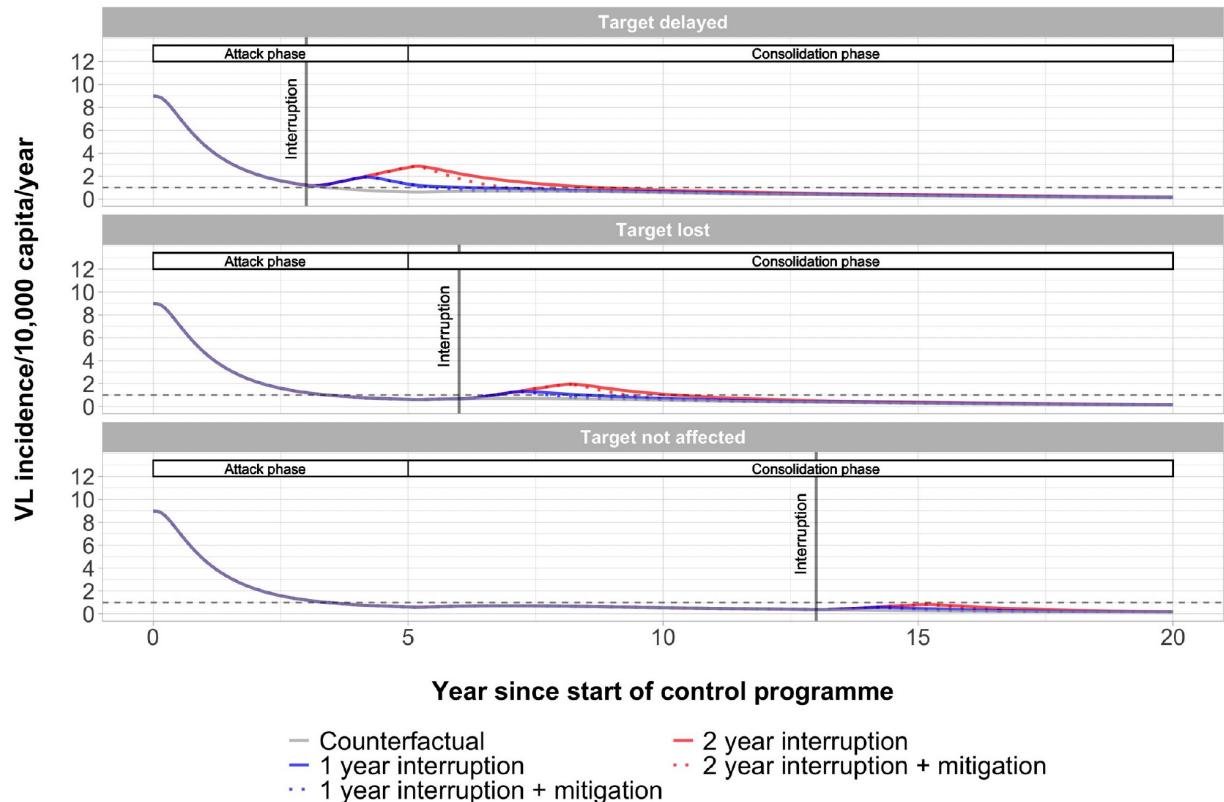


Example 4

- What is the impact of COVID-19 related interruptions of VL control on feasibility and sustainability of the control targets?



Modelling the impact of COVID-19-related programme interruptions on visceral leishmaniasis in India



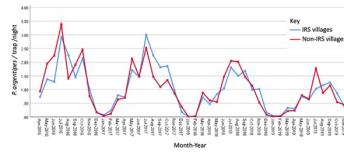
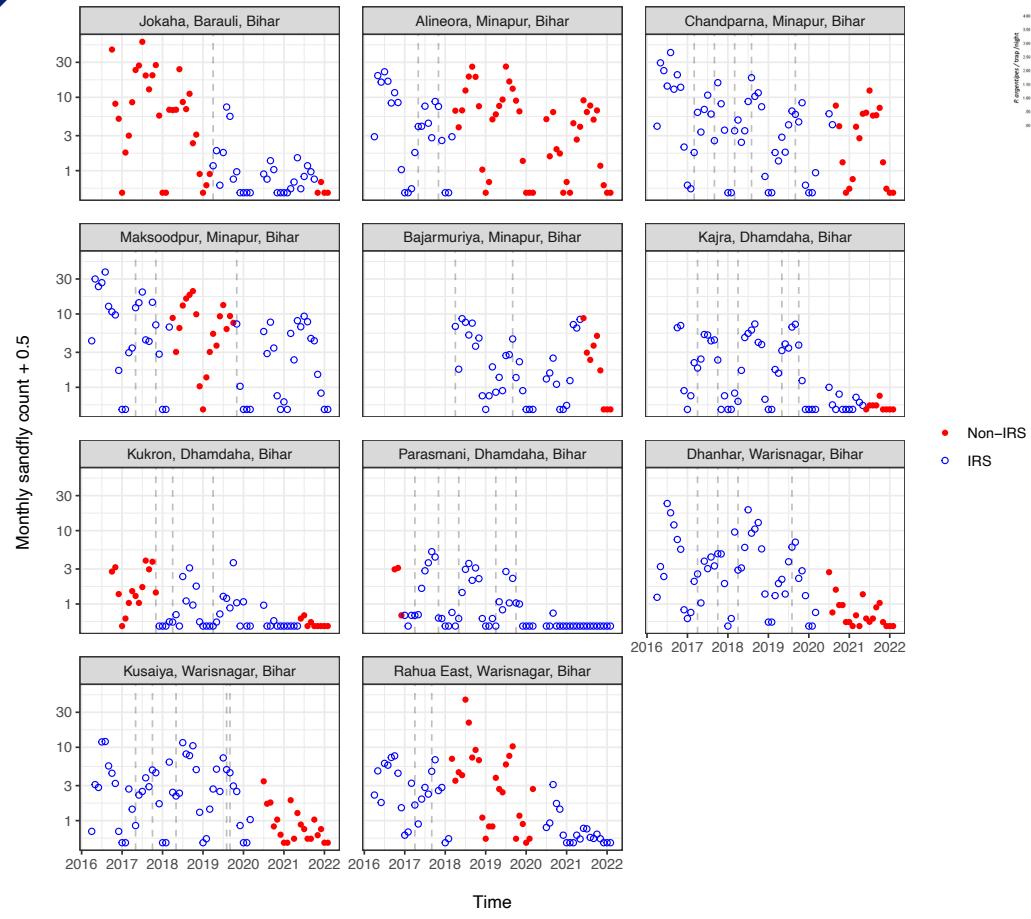
- Deterministic model
- Characterise the delay in achieving the control targets for a range of settings (duration of control thus far) and mitigation strategies.



Example 5

- What has been the impact of IRS on sandfly abundance and VL case incidence? (ongoing)
 - How do sandfly abundance and impact of IRS depend on housing conditions?





UNPUBLISHED – ONGOING WORK

- Collaboration with LSTM based on existing study data from Bihar, Jharkhand and West-Bengal (Deb et al. 2021 PLoS Negl Trop Dis)
- Statistical analysis of vector abundance data 2016-2022 (interrupted time series analysis)
- Linked to new data on housing conditions
- Deterministic and stochastic model versions to predict impact of IRS, conditional on estimated effect from statistical analysis
- You will be using this model as a template during later exercises



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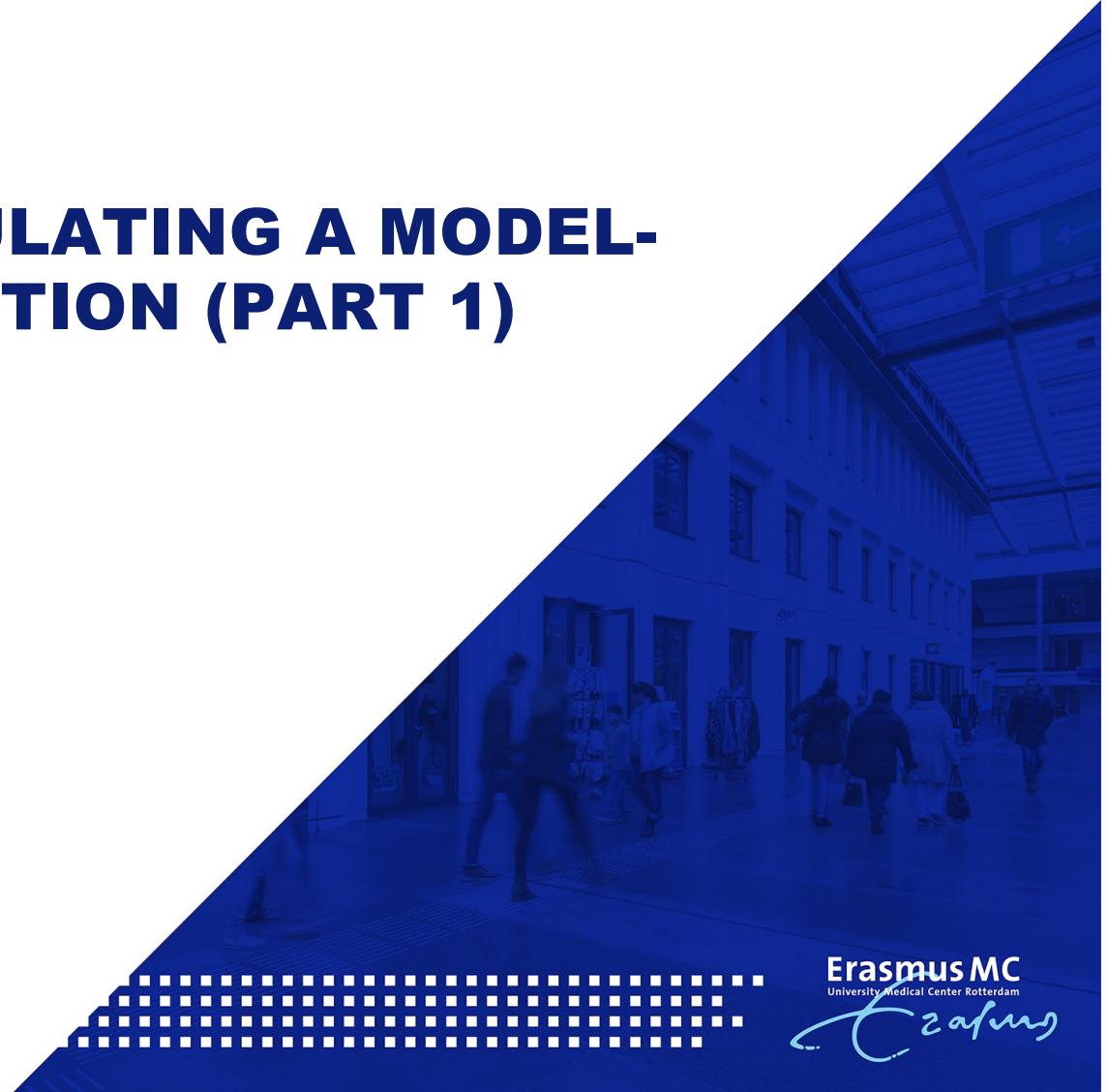
10:45 – 11:00 am

TEA BREAK

**(PLEASE COME BACK WITH YOUR TEA
FOR AN EXERCISE IN PAIRS)**

11:00 – 11:15 am

BREAK-OUT: FORMULATING A MODEL-ANSWERABLE QUESTION (PART 1)





Break-out instructions

- 15 minutes
- Split into pairs
 - Partner up with someone with a different expertise/background than your own
- Each partner takes 5 minutes to themselves
 - Formulate a research question
 - Addressing a gap in the control of VL
- Discuss with partner for 10 minutes and agree on a research question

Doesn't need to be perfect yet. We will revise and discuss formulated questions in the next break-out





Open questions (examples)

- Role and value of potential new PKDL diagnostics and treatments in VL control
- Role and impact of IRS as currently implemented (reactive to case incidence) – ongoing project
- Role and impact of human mobility on VL as a walking epidemic and implications for control strategies near/after reaching control targets
 - Most existing modelling studies consider VL to be at a endemic equilibrium (at a high geographical scale) and ignore spatiotemporal heterogeneity
 - Very hard to address – not suitable for this 2-day workshop, although first steps towards this may be undertaken
- Role and impact of HIV infection and its treatment on transmission and control of VL
- ...

11:15 am – 12:15 pm

DEVELOPING COMPARTMENTAL MODELS





Views and expectations about models from non-modellers

- When and where will the next outbreak be and how big it will be?
- Are current control approaches effective or can they be improved?
- Model results are confounded because socio-economic factors are not included
- Modellers don't know the realities of day-to-day work in the field and the issues with the quality of the data
- Sometimes what the authors concluded and wanted to convey is not actually conveyed in the sense that they wanted to. Many of the programme people will take the conclusions literally





PRIME-NTD: good practice in model development

Policy-Relevant Items for reporting Models in Epidemiology of Neglected Tropical Diseases

1. Stakeholder engagement
2. Complete model documentation
3. Complete description of data used
4. Communicating uncertainty
5. Testable model outcomes

What has been done to satisfy each principle?

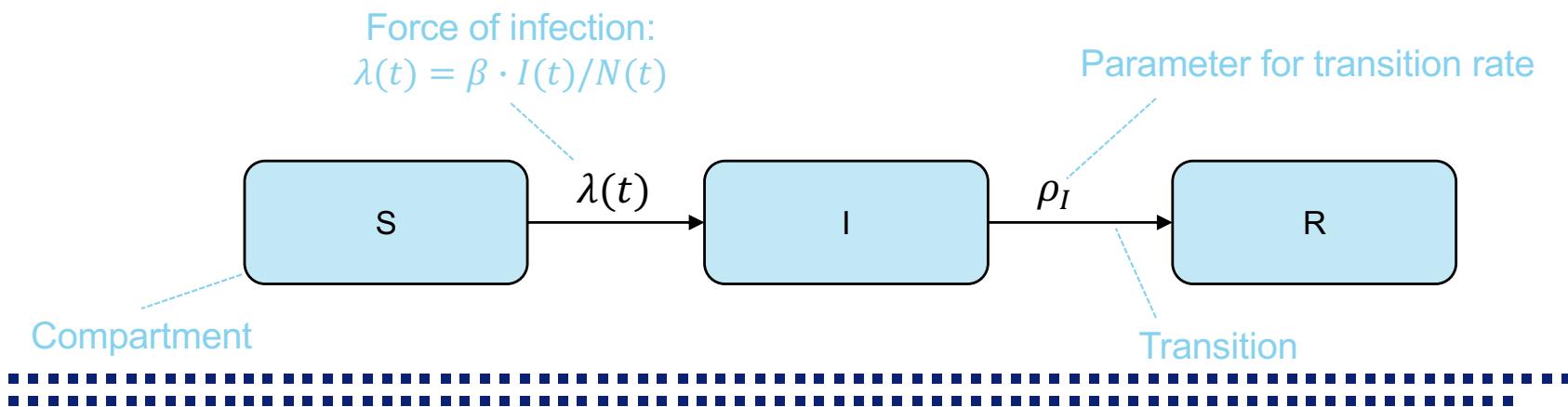
Where in the manuscript is this described?

Standard part of reporting models within the NTD Modelling Consortium



Compartmental models

- Represents a population (or a cohort of individuals that is part of some larger population)
- Describes mutually exclusive health states and transitions between them
- Transitions are defined in terms of rates (durations per compartment are exponentially distributed)
 - Optional: fractions by which to split transitioning individuals over multiple transitions
- Implemented as a system of ordinary differential (or difference) equations (ODE)





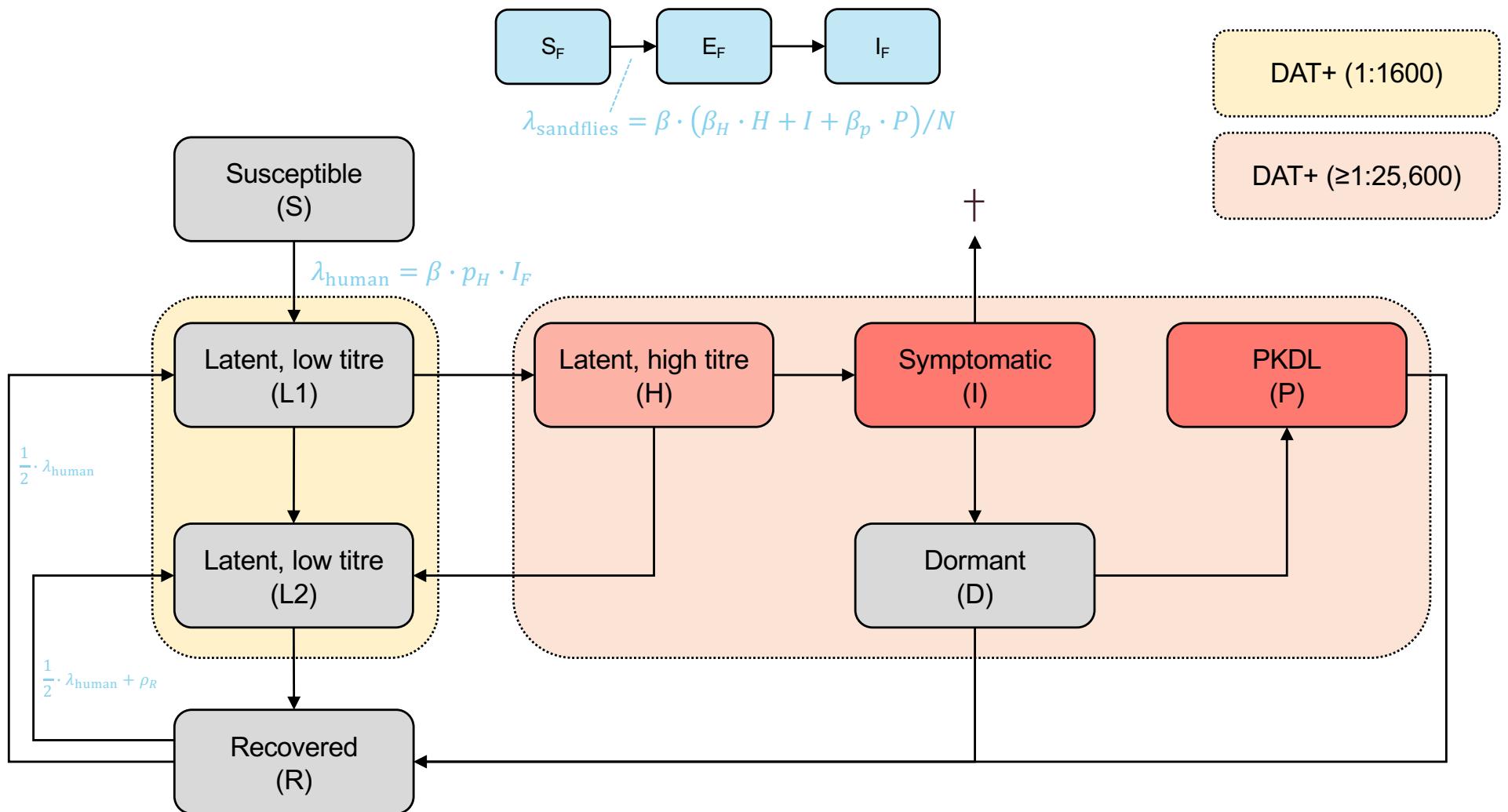
Compartmental model for VL

Human population (single population, no age explicit structure)

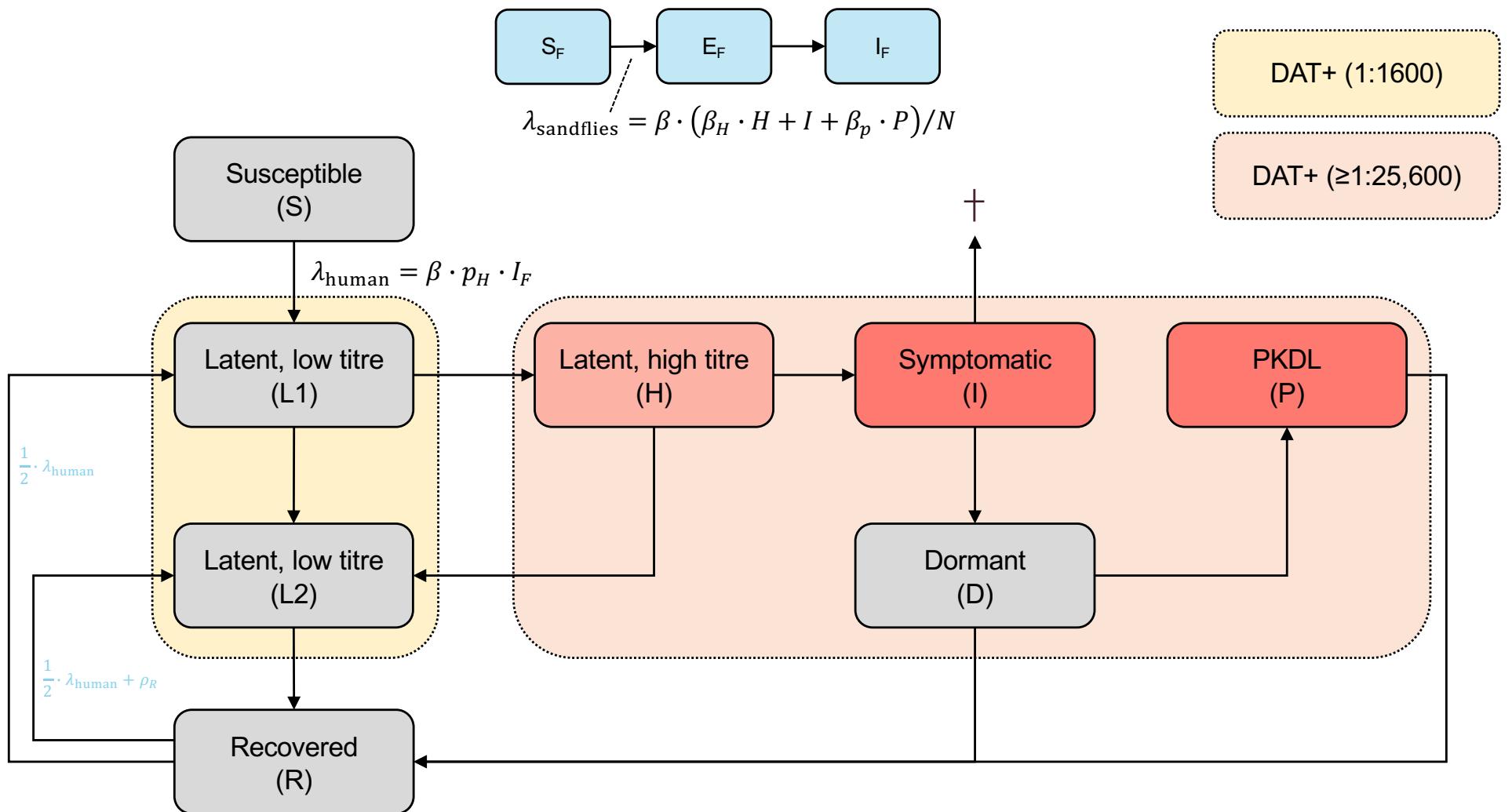
- Susceptible population
 - Infected at a rate depending on the number of infectious sandfly bites per human per time unit
- Asymptomatic and potential development into symptomatic infection
- Recently treated individuals (dormant infection)
- Recovered (treated and no longer at risk of developing PKDL)
- PKDL
- Birth, death due to untreated VL, and death due to other causes
 - Stable population size by letting birth equal total number of deaths

Fly population (defined in terms of “effective number of flies” per human)

- Susceptible, exposed, and infectious flies
 - Infected at a rate depending on the number of susceptible sandfly bites on infected humans per time unit



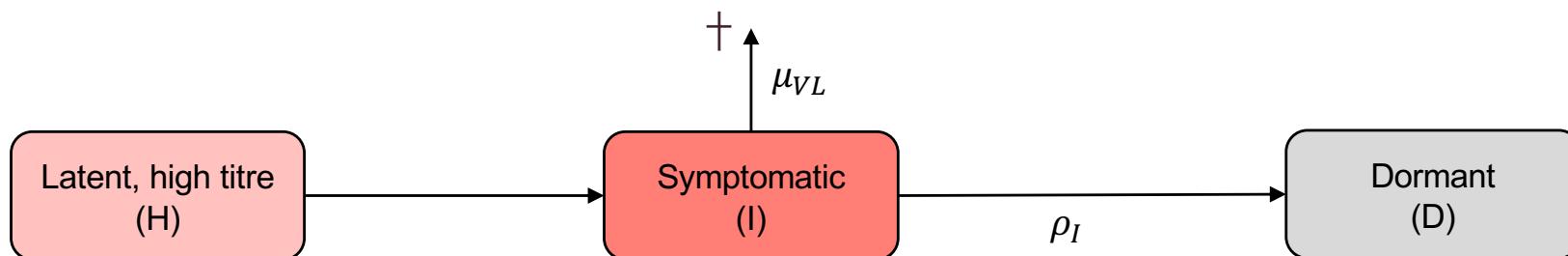
Not shown: human births (into S); deaths due to other than VL (from all compartments); birth rate of sandflies (into S_F) or impact of IRS on sandfly birth rate.



Not shown: human births (into S); deaths due to other than VL (from all compartments); birth rate of sandflies (into S_F) or impact of IRS on sandfly birth rate.

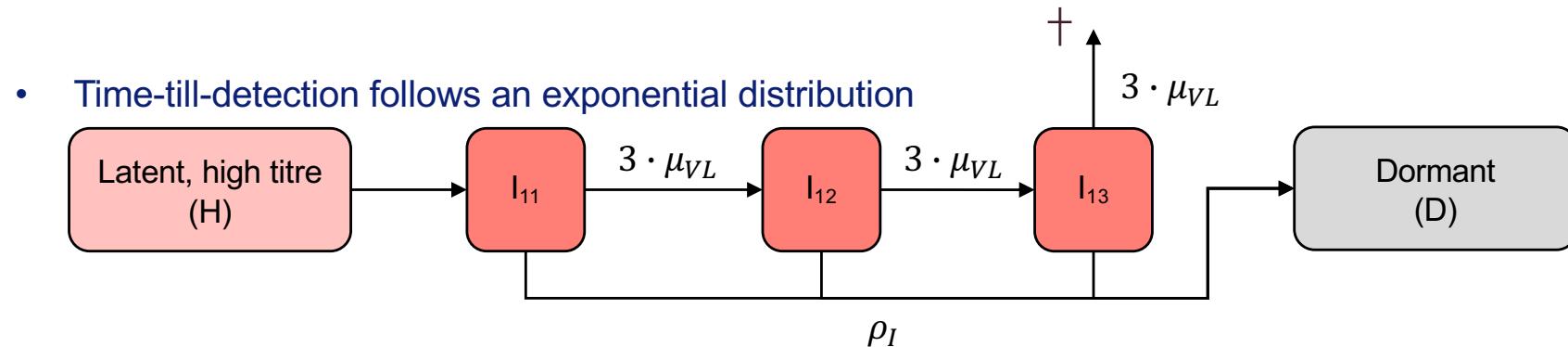
Non-exponential processes

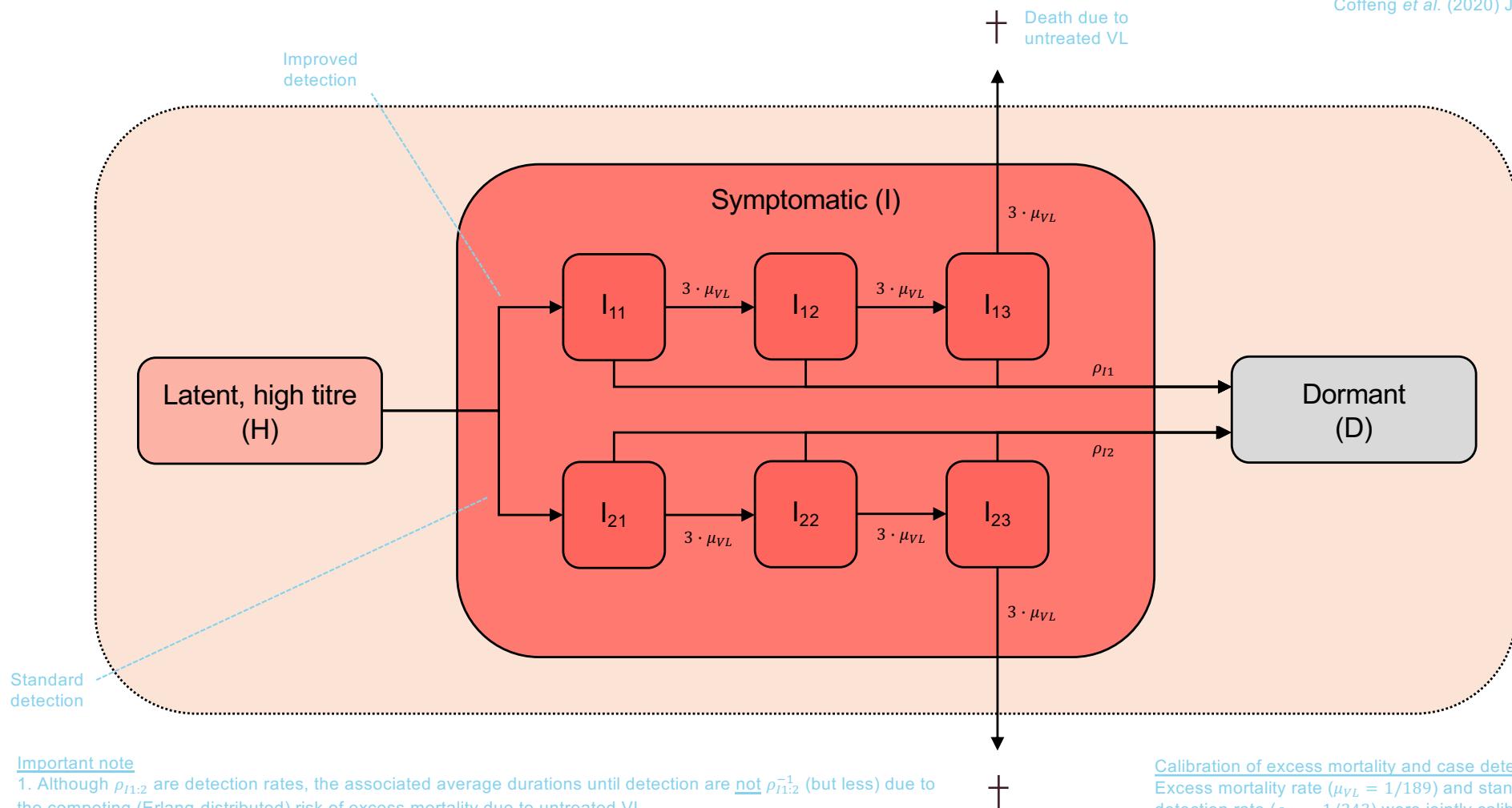
- Time-till-event is exponentially distributed in simple compartmental models
- Not realistic for death due to untreated VL: risk increases over time (with VL infection)
- Time-till-detection/treatment may also not be exponentially distributed, but likely still closer to it than death due to VL



Solution for simple ODEs: Erlang distribution

- Erlang distribution = gamma distribution with shape parameter k of integer value
 - k = equal to number of serially chained exponentially distributed compartments
 - Transition rate between chained (and out of last) compartments is $k \cdot \frac{1}{\text{average duration}}$
(in absence of competing rates)
- Time-till-death following an Erlang($k = 3$) distribution
 - $k = 3$ approximates a Weibull distribution with shape 2 (= linear increase in rate over time)

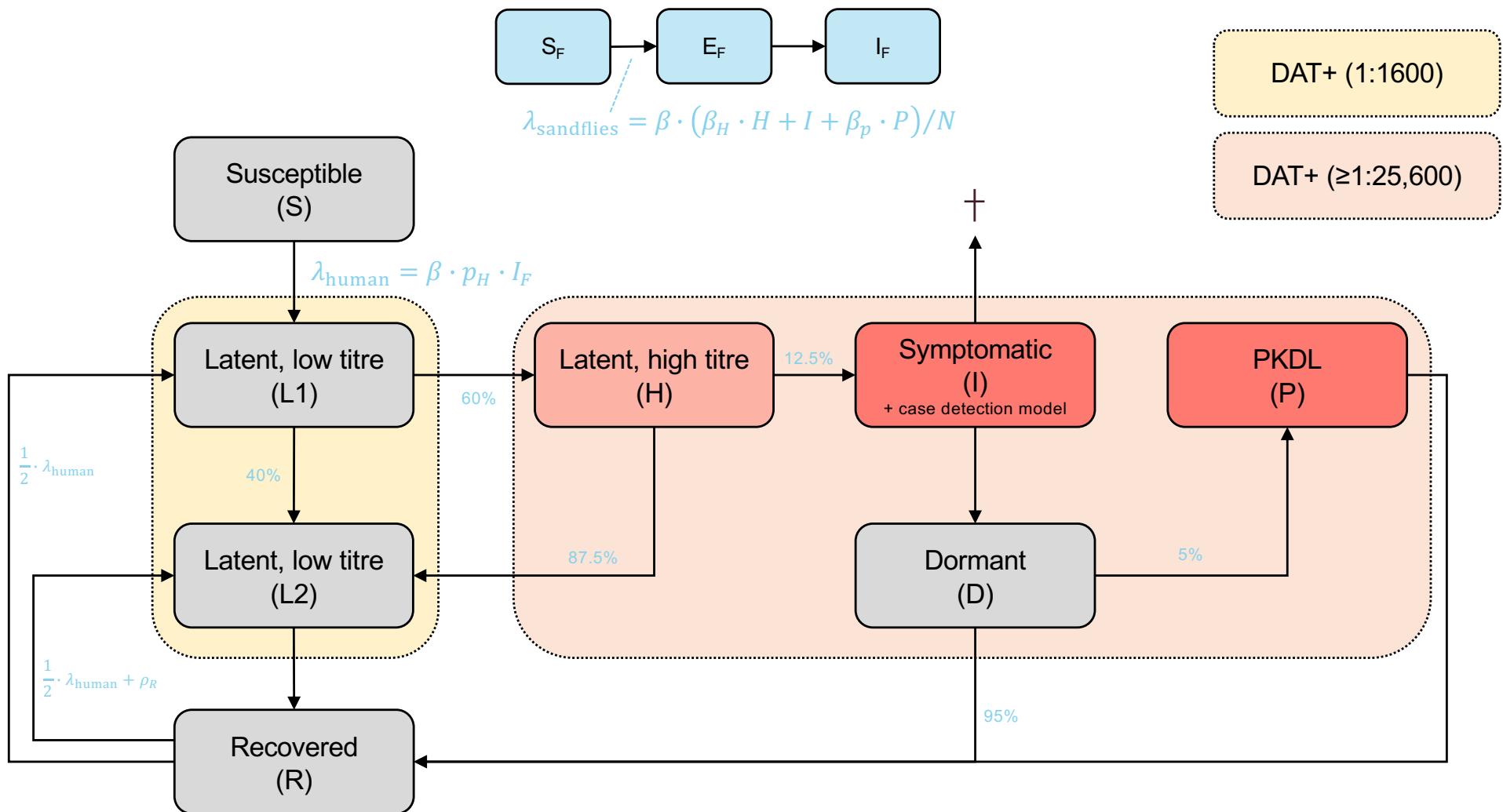


Important note

1. Although $\rho_{I1:2}$ are detection rates, the associated average durations until detection are not $\rho_{I1:2}^{-1}$ (but less) due to the competing (Erlang-distributed) risk of excess mortality due to untreated VL.
2. Excess mortality rate μ_{VL} is the same for all individuals, but the effective mortality depends on whether an individual is covered by improved (ρ_{I1}) or standard (ρ_{I2}). The average duration till death among cases who die due to untreated VL is not μ_{VL}^{-1} (but less) due to the competing (exponentially distributed) time till detection.

Calibration of excess mortality and case detection

Excess mortality rate ($\mu_{VL} = 1/189$) and standard detection rate ($\rho_{I2} = 1/243$) were jointly calibrated such that 50% of VL cases die undetected after an average of 150 days, and detected cases experience an average detection delay of ~90 days.



Not shown: human births (into S); deaths due to other than VL (from all compartments); birth rate of sandflies (into S_F) or impact of IRS on sandfly birth rate.



Deterministic implementation: assumptions and considerations

- Infinitely divisible population
- Numerical integration over continuous time (approximately)
- Sufficient for understanding basic characteristics of the system of ODEs
 - Equilibria
 - Break-points
 - Implied age patterns
 - System sensitivity to perturbances
- Not good for:
 - Simulation of probabilities (e.g., elimination or outbreak risk)
 - Representing small populations



Implied age patterns

- Models without explicit age structure still imply an age pattern in infection dynamics
 - Can be investigated with “cohort version” of the model
- Consider: system of ODEs as representation of a cohort of newly borns, born at time $t = 0$
 - No new births
 - Decreasing population size as individuals age and die over time
 - Fixed force of infection (as a parameter and not as a function of the population state; also referred to as “external force of infection”)
- The state of the system at time t can be taken to represent the state of the cohort at age t



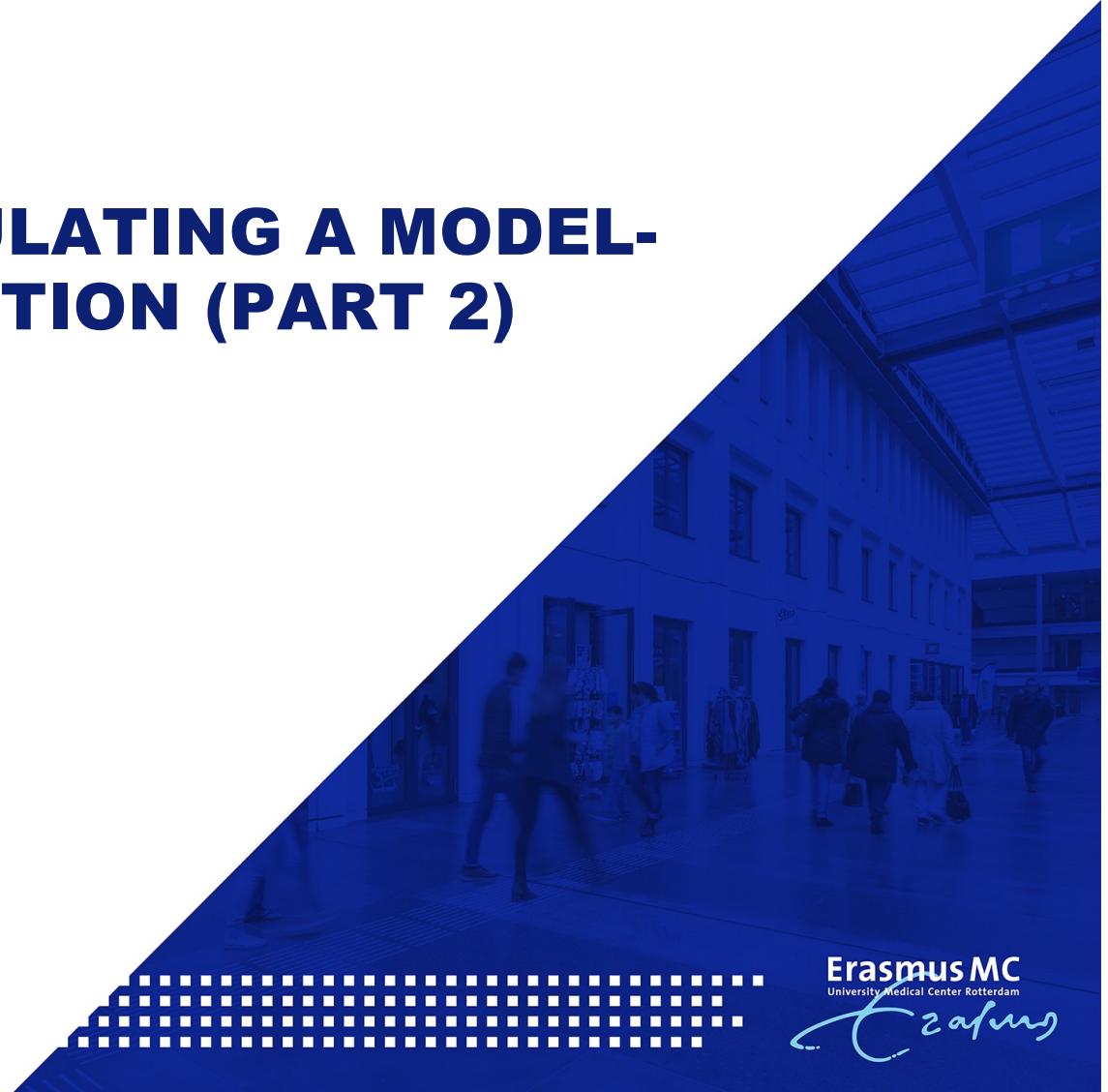


Stochastic implementation: assumptions and considerations

- For when a deterministic model does not suffice
 - Finite population with discrete number of individuals
 - Good for simulation of probabilities and small populations
- Discrete time steps (i.e., the version we'll cover here)
 - Rates must be translated to probabilities
 - Time steps must be sufficiently small to be able to consider rates more or less stable over the period covered by a time step
- Higher programming effort (and risk of bugs)
 - During model development: compare behaviour to deterministic implementation
- Higher computational effort
- Basis for more complex models (covered on day 3)

12:15 – 12:45 pm

BREAK-OUT: FORMULATING A MODEL-ANSWERABLE QUESTION (PART 2)





Break-out instructions

- 30 minutes
- Combine with another pair to form a team of 4
 - Ideally, every group has at least 2 people who are familiar with programming in R
- Choose one question per group, considering:
 - Is the question model-answerable?
 - How can it be represented in a compartmental model?
 - Do not (yet) worry about data needs
- Draw a schematic diagram for your model (extension)
 - Do you need new compartments and/or transitions between compartments?
 - If not, how would you use the provided VL template model?
- Prepare two slides with (1) the question and (2) the model structure (send slides to the workshop trainers)
- Select one person per group to present the slides (after lunch)
 - 3 min pitch + 12 minutes plenary discussion per group

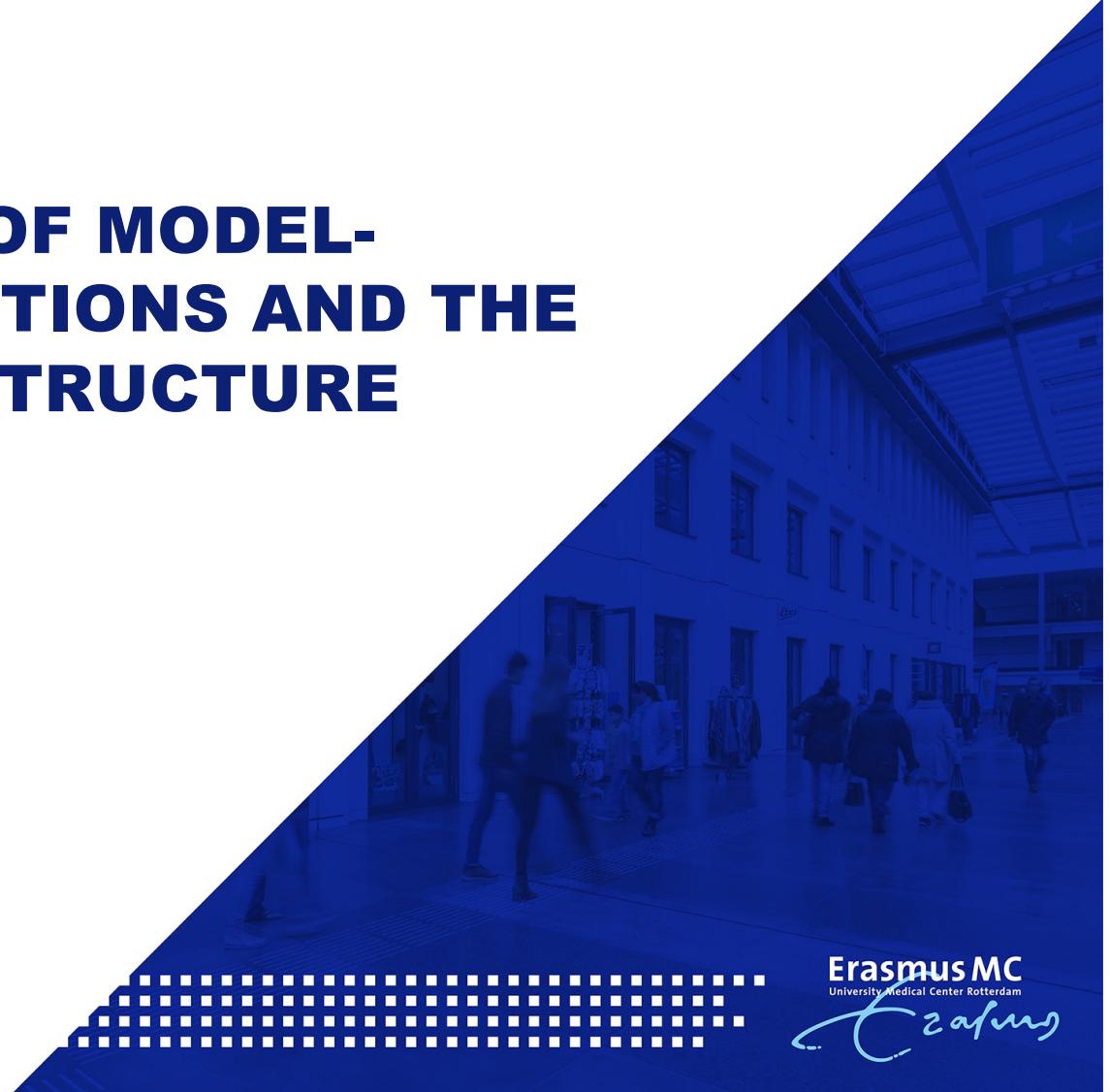
12:45 pm – 2:00 pm
LUNCH BREAK



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University Medical Center Rotterdam


2:00 – 3:30 pm

PLENARY PITCHES OF MODEL- ANSWERABLE QUESTIONS AND THE REQUIRED MODEL STRUCTURE





Plenary pitches

Per group: 3 min pitch + 12 minutes plenary discussion

- Data needs will be discussed during the next session

If time left: example question and model (pitch by Ananthu)





Take aways from discussion

We worked on

- Translating the question to a model
- Spotting implied assumptions
 - (Non-)identifiability of individuals with particular characteristics if they are not allowed to have their “own sub-model”
- Relevance of mobility depends on context
 - What type of areas? How different and in what respects?
- Using an existing model creatively by re-interpreting its meaning
 - Introduction of a PKDL case in a non-endemic population can be accomplished by simply putting a single PKDL individual in that compartment. No need to simulate mobility



3:30 – 3:45 pm
TEA BREAK



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University Medical Center Rotterdam
Erasmus

3:45 – 5:00 pm

DATA NEEDS AND AVAILABLE DATA

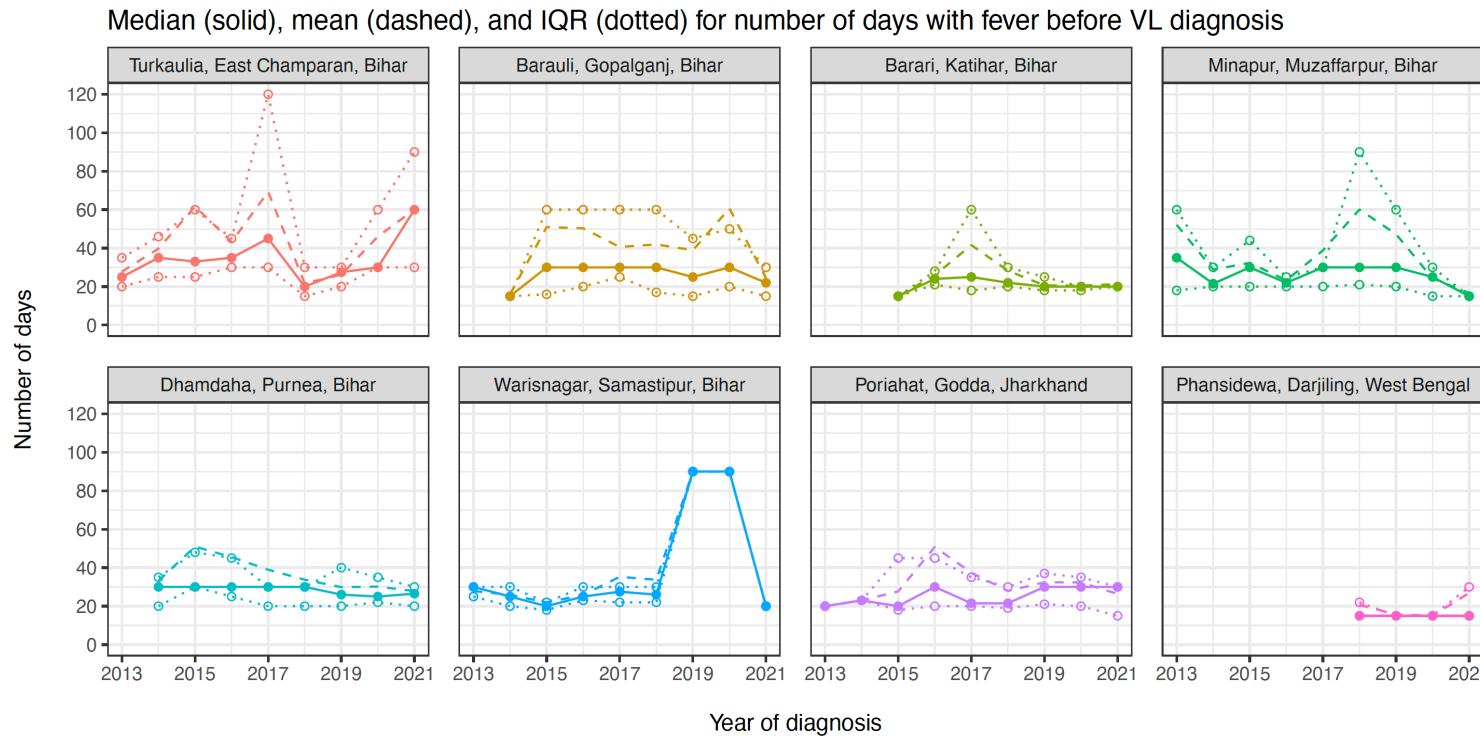




Data used for modelling so far

- Literature data (hand-out provided)
 - Disease biology
 - Sandfly biology
 - Epidemiological data (e.g., age patterns in infection and antibody positivity)
- Case data (since 2013 curated in KAMIS)
 - Village-level since 2013
 - Only block-level data before 2013
- Sandfly data on abundance and infection rates, but several challenges:
 - What do such data actually represent and how to link to model?
 - Infection rates in sandflies are extremely low
(Deb et al: only a few infections among >100,000 caught flies)
 - Only available for particular study sites (e.g., Deb et al. 2021 PLoS Negl Trop Dis)

Detection delay data in KAMIS (example)



Challenges in data access

- KAMIS case data
- Programmatic data on implementation of IRS and sandfly abundance
- Data on human mobility
- Mortality data (non-existent?)
- Programmatic populations surveys towards/during/after reaching the control targets (non-existent!)

ALWAYS: data are never perfect, so be careful how much stock to put into them

Dealing with lack of data

- Involve experts (#1 in good model development practice - Behrend *et al.* 2020 PLoS Negl Trop Dis)
 - Clinical / entomological / epidemiological expertise
 - Control program field staff & management (What is actually happening in the field? What is feasible?)
 - Policy makers (What are the current questions?)
- Use model to explore implications of uncertainty for answers to questions! (What if....?)
 - Scenario analyses (change a parameter, then recalibrate model and repeat analysis)
 - Sensitivity analyses / uncertainty quantification (change parameters without recalibration)
- Try to answer: which data should be collected/available and how and why?

Plenary discussion

- Data needs for each of the 5 pitched models
- Strategies to deal with lack of data

Plan for day 2

- Recap + opportunity for questions about
 - Any of the talks so far
 - The template VL model
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- Build a deterministic (and, if you can, stochastic) implementation of your conceptual model
 - In R, with the *pomp* package
 - Make sure you have installed the *pomp* package and checked it worked
 - Recommended: also install and work in Rstudio
- Preparation:
 - Download files from public repository and have a look at the file “Model Description.pdf”:
<https://github.com/Ananthu89/NDMC-VL-Workshop-IITB-2023>
 - Install pomp in R (if not done already): <https://kingaa.github.io/sbied/prep/>