Visceral leishmaniasis (VL) in the Indian sub-continent (ISC)

epidemiology, dynamics, control and elimination

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NTD MODELLING CONSORTIUM

- Address the epidemiological question: “Are we on target for the 2020 goals with current strategies”
- If not, what other strategies will be required, and where?
- A tool in the international collaborative effort to control NTDs
- BMGF Funding (Novartis Foundation for Leprosy):
  - Nine diseases
  - Two groups per disease
    - Scientific robustness
    - Investigate underlying assumptions
  - To provide a coherent, consensus analysis for policy

Interventions for NTD

- No vaccines
- Mass Drug Administration (MDA)
  - Requires “free”, safe drugs – not for VL
- Intensive Disease Management (IDM)
  - Requires diagnosis and timely treatment
  - Both have improved substantially for VL, but not ideal
- Environmental interventions
  - Indoor Residual Spraying (IRS)

"…a warning of the danger to those who try to speak without sufficient knowledge, or on ground with which they are unfamiliar. "

Sir Harold Scott, President of RSHTM, in response to a paper read by H.E. Shortt, *Recent Research on Kala-Azar in India*, 17 May 1945

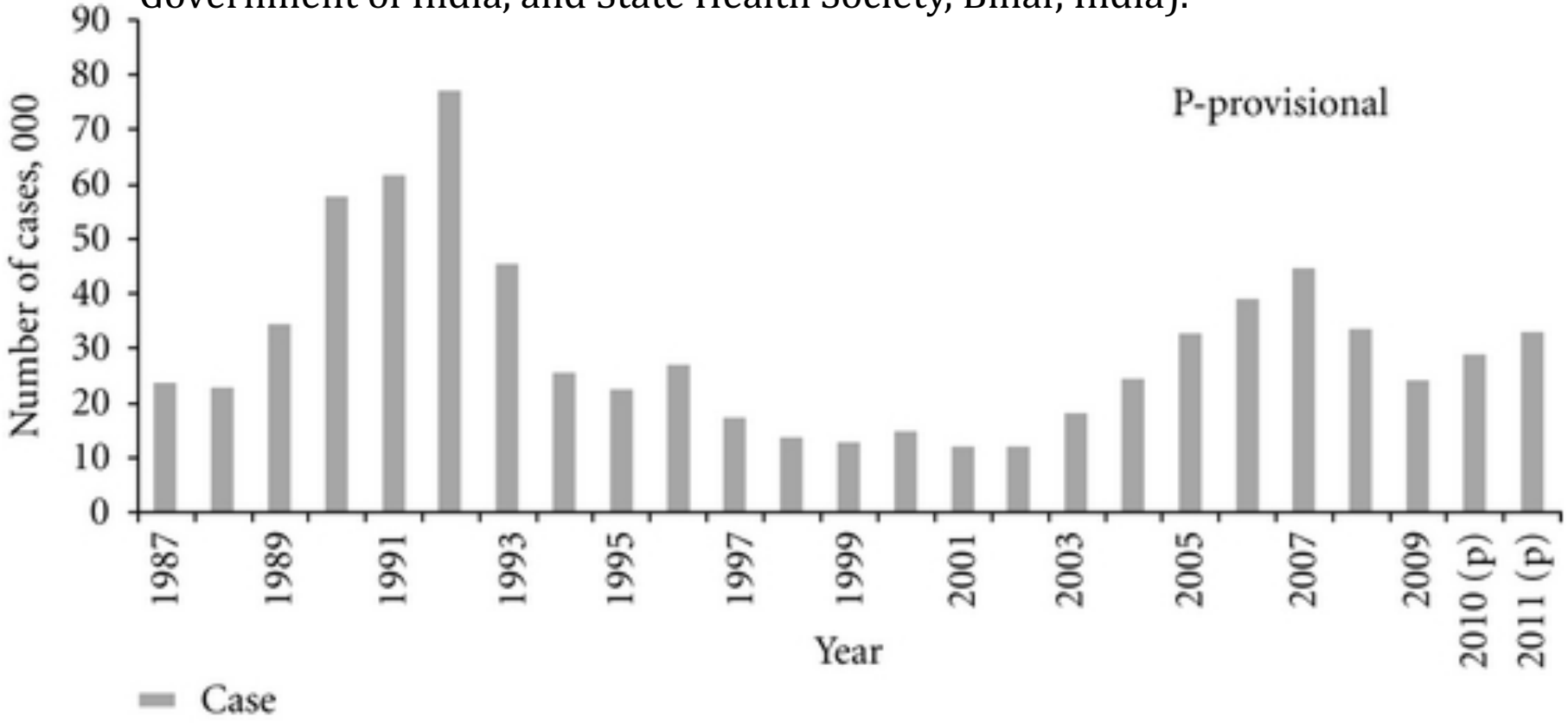
Natural & Clinical History of VL

- Very little is known with quantitative accuracy
  - Variation in species, and across geographical areas
  - Poor diagnostics
  - Unspecific clinical symptoms
    - Fever, weight loss then splenomegaly & anaemia
  - Unknown proportion asymptomatic infection
  - No estimates of relative infectiousness of KA and PKDL (and latent etc)
  - No good, longitudinal (>5yr) data on diagnostic, epidemiological and clinical outcomes
- Impossible to build a traditional model based on literature estimates of biomedical processes

- Symptomatic (KA) cases are a small minority of infections
- Do they contribute the most to transmission?
  - Nepal and Bangladesh have shorter infection to treatment times than Bihar
    - Enough difference to explain difference in incidence
  - VL demonstrates some long-term cyclic behaviour
    - SIR type dynamics rather than SIS
  - KA is highly spatially and temporarily clustered
    - Suggests that KA "creates" KA locally
  - Evidence that DDT-based IRS has not been effective

- Suggests that earlier treatment of KA cases has a disproportionate impact on transmission

Kala-azar cases in India during the period from 1987 to 2011
(source: Directorate General of Health Services, (NVBDCP), Government of India, and State Health Society, Bihar, India).



Kalanet trial (Ostyn 2011) 2.4/1000 PY in those without Previous signs/symptoms of VL
In DAT negatives (9034) before trial started 2.8/1000 PY

SPEAK India

- New BMGF Consortium: LSHTM role is to facilitate
- Focus on
  - knowledge to inform operational strategy
    - Achieve elimination
    - Sustainably maintain elimination
  - concerted, co-operative action
    - Consensus of current knowledge
    - Consensus of required research

VL Targets

- Elimination as a public health problem
  - < 1/10,000/year cases in small areas
  - Still a large number
  - But asymptomatic infection will remain and resurgence likely to be a problem
- Nepal & Bangladesh are close to “elimination”
  - Nepal was hoping for declaration 2016 or 2017
- Bihar remains higher (~5 / 10,000 per year)

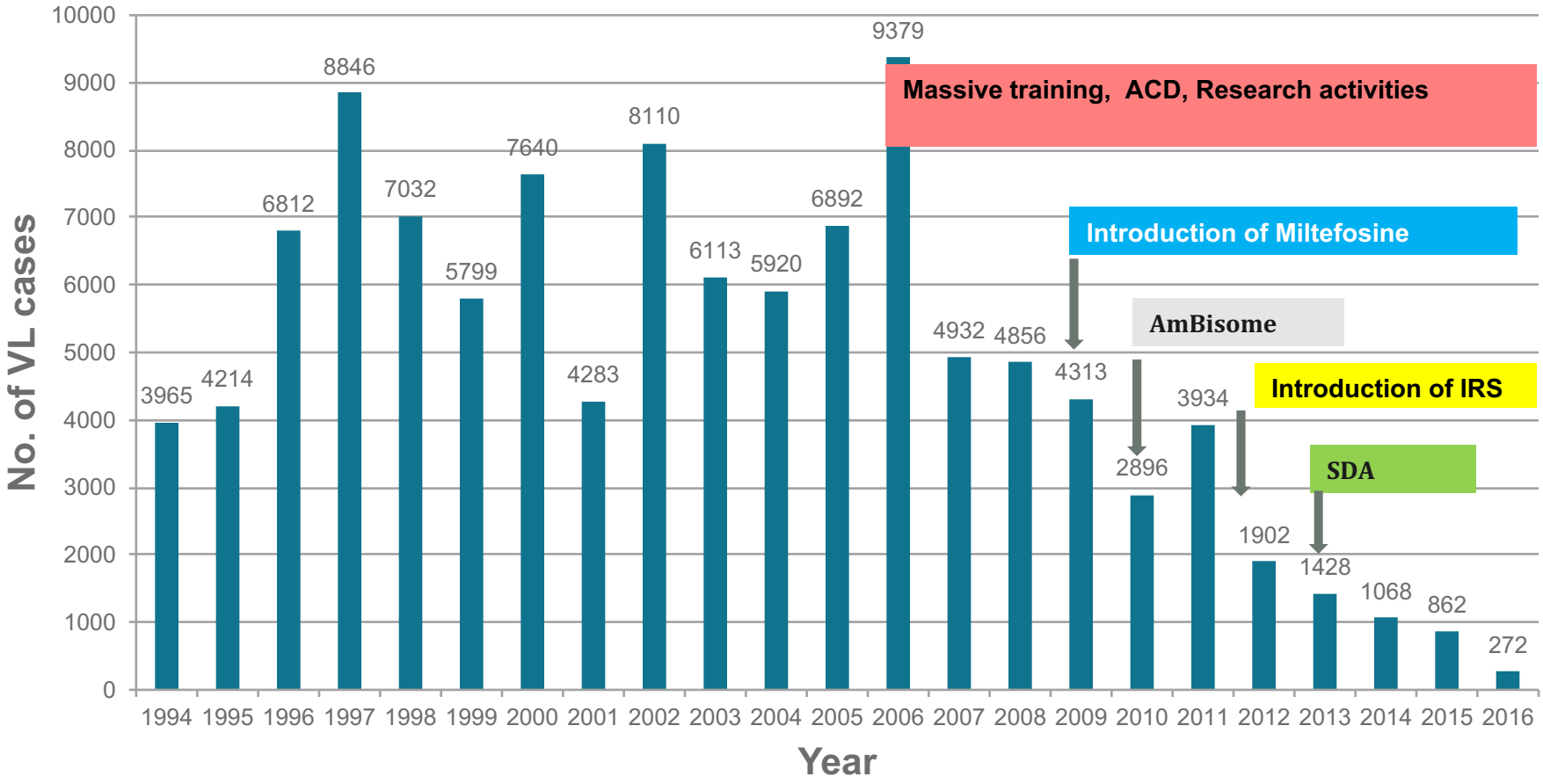
Issues / Questions

- Elimination as a public health problem
  - This is really (formally) “control” at a low level
  - The low level achieved is dependent on the intervention
  - Relaxation of intervention will result in resurgence
- IRS & IDM
  - Which is the most important?
    - i.e. which should we maintain post-elimination
- Focal interventions
  - How can spatial patterns be exploited?

1. Decrease in Cases

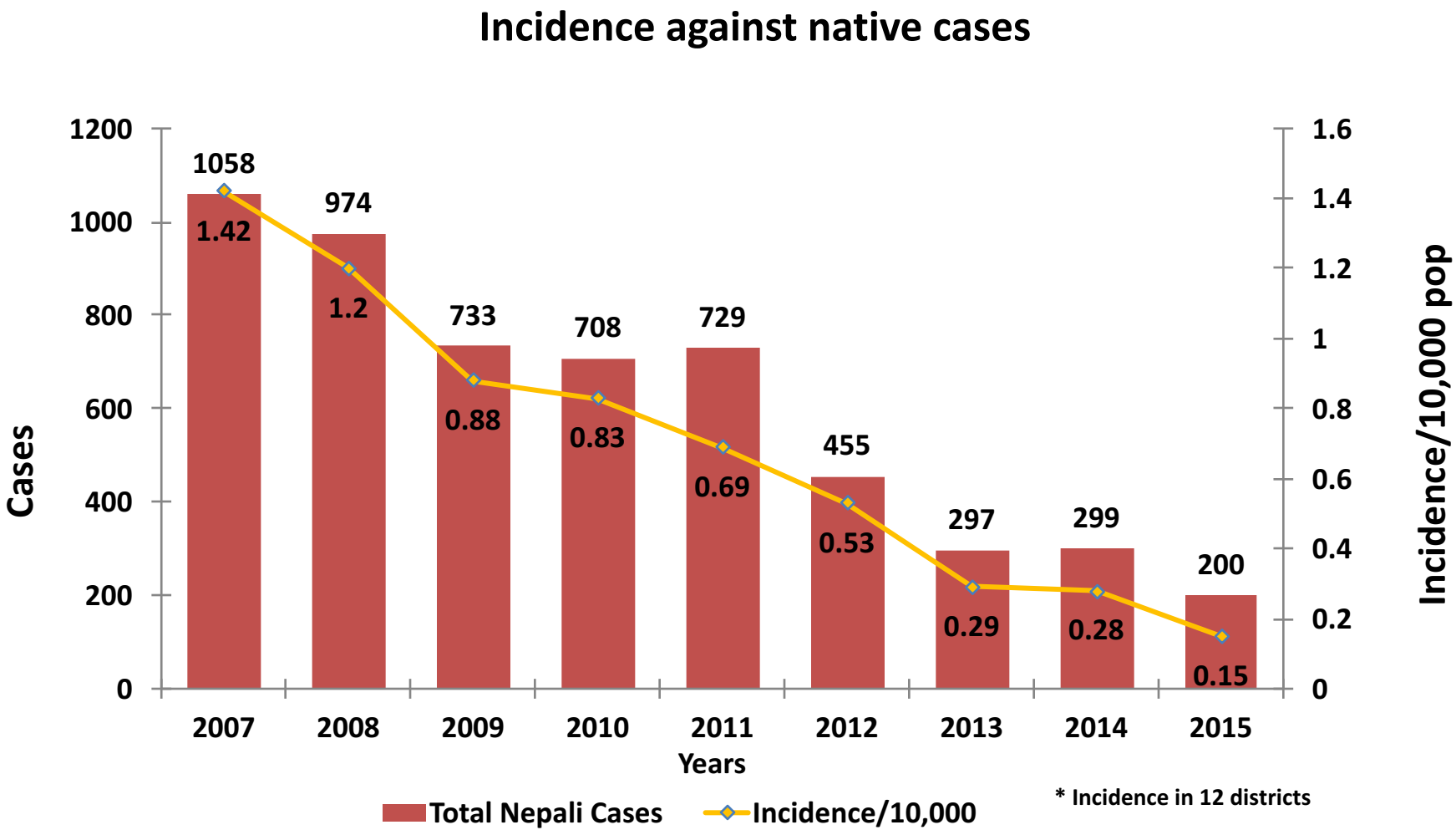
- The time series of diagnoses shows a decreasing incidence
  - IDM (higher, faster coverage of treatment)
  - IRS (reduced transmission)
  - Both
- Does the pattern give us any clues?

Trend of VL in Bangladesh (1994-2016)

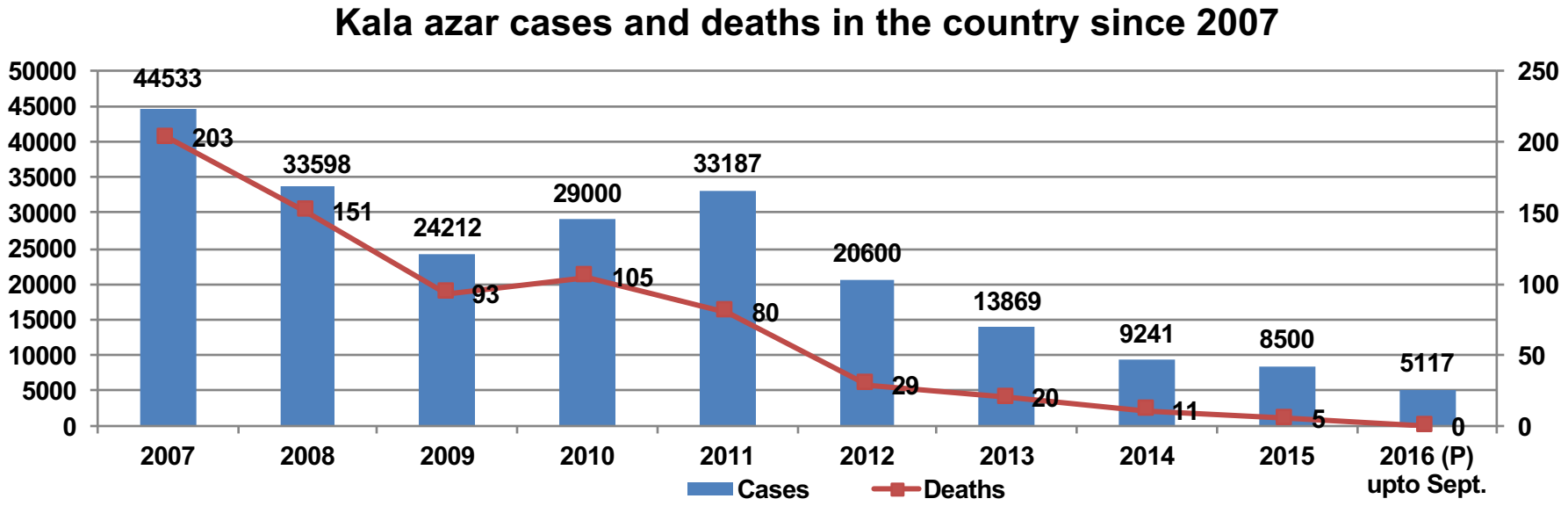


In 2016 all VL endemic Upazila is going to have VL case number less than 1< 10,000 people in Bangladesh

National Annual Incidence: 2007-2015



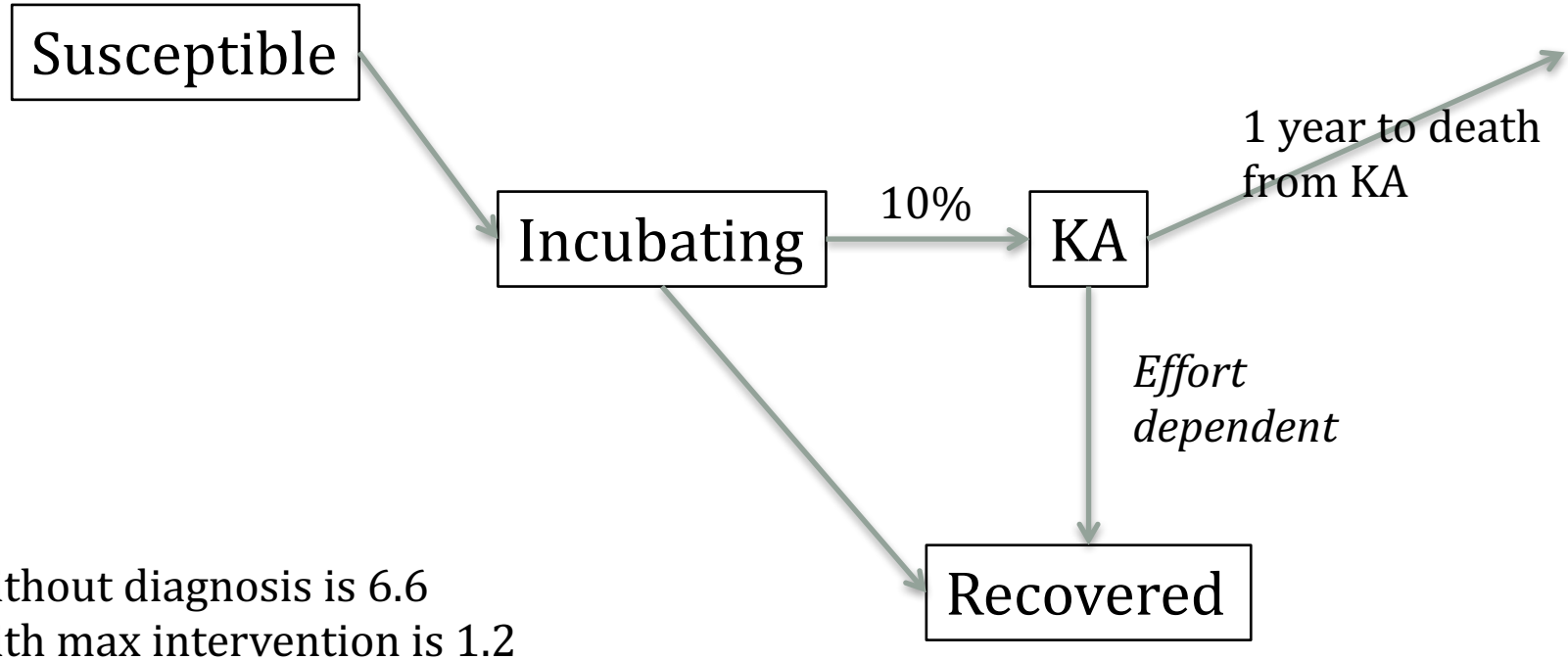
Achievement



- **Road Map for KA Elimination launched in Sept 2014 with timeline**
- **Single-day single-dose injection of Liposomal Amphoterecin B (LAMB) for treatment of Kala-azar introduced in 2015.**
- **Synthetic Pyrethroid introduced for Indoor Residual Spray (IRS)**
- **Development Parners involved viz.BMGF-CARE, Kalacore consortium**
- **Out of 628 Kala-azar endemic blocks, 492 (78%) endemic Block PHCs have recorded annual incidence rate of < 1 case per 10,000 population at Block PHC level in 2015**

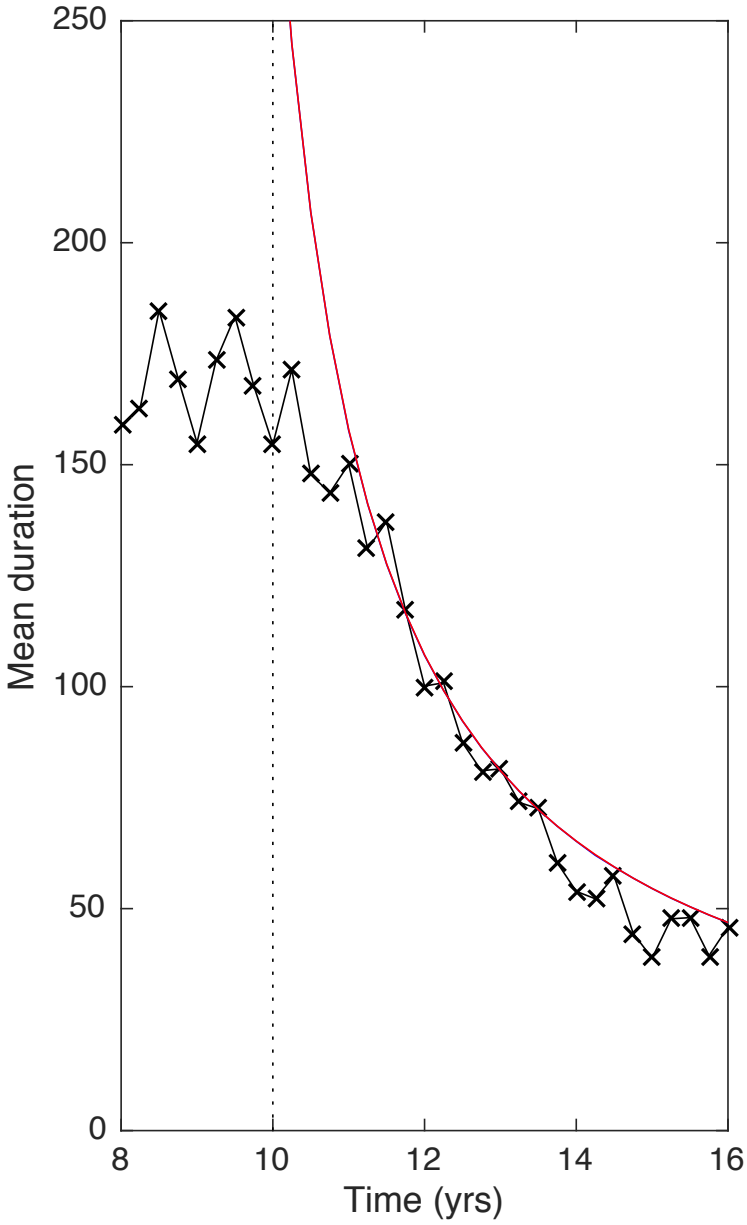
Simple Model

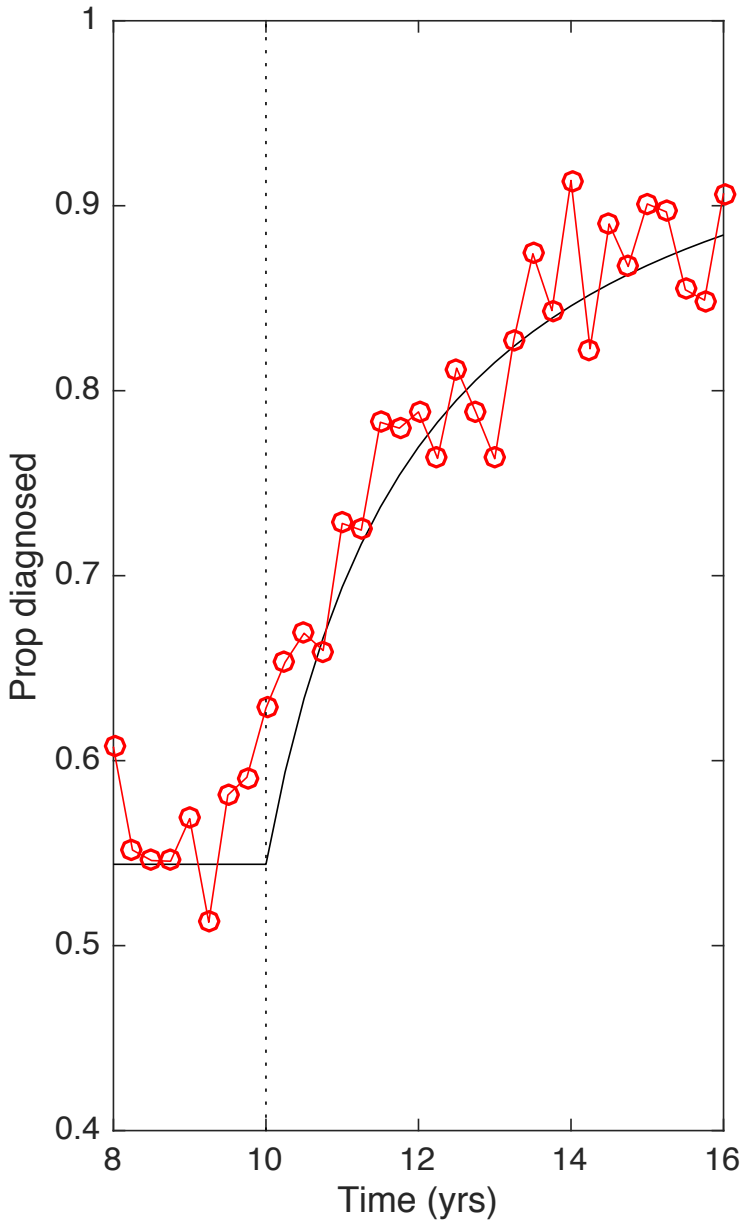
- Infection leads to disease in a minority
- Disease leads to death in all
- Diagnosis leads to treatment and recovery
- The “effort” put into diagnosis creates a competing risk between diagnosis and death
- The more effort put into diagnosis, the “younger” cases are when diagnosed and the more are diagnosed
  - Think fishing…
- The actual number of disease cases is never observed: we only see the diagnosed

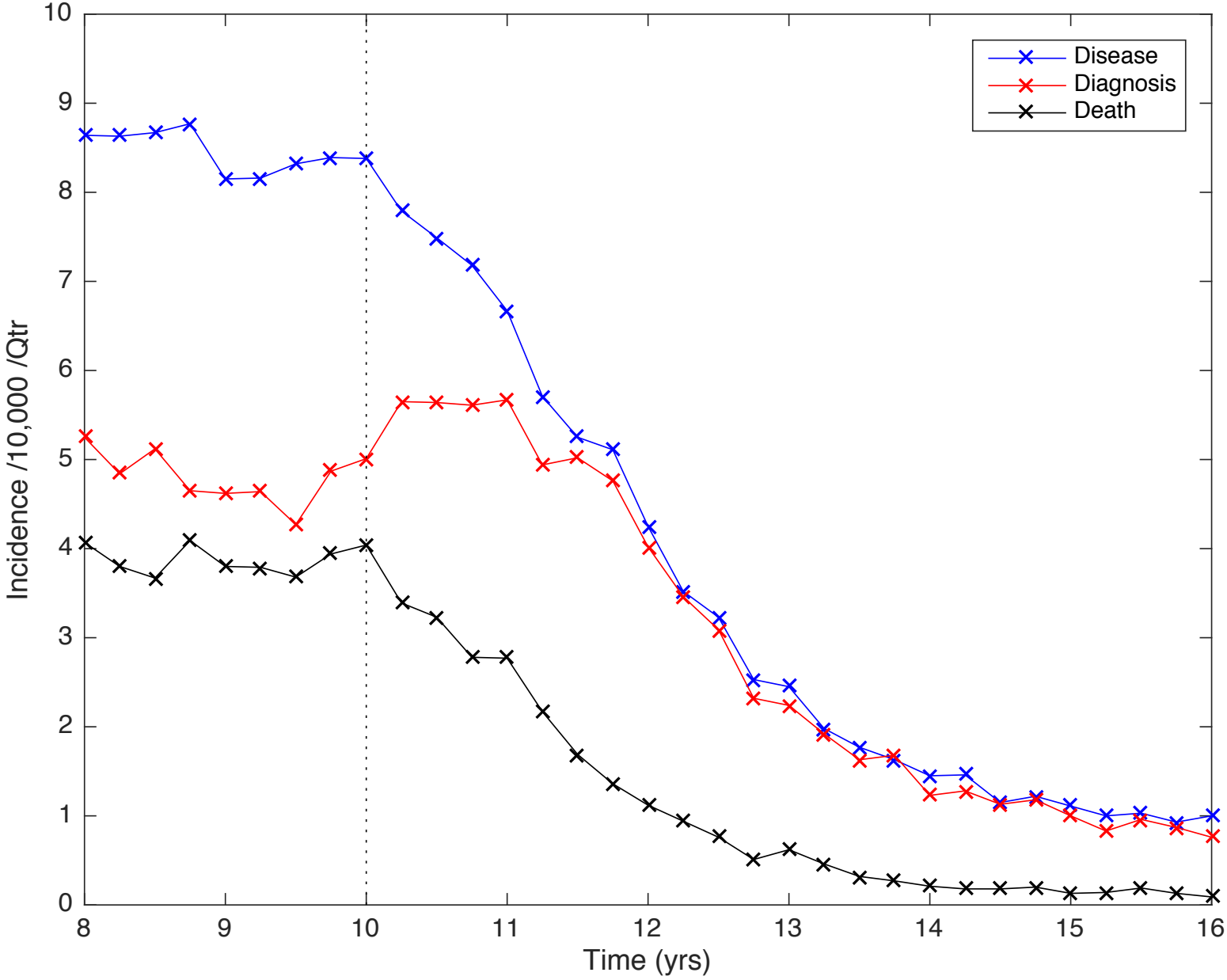


R_0 without diagnosis is 6.6
R_0 with max intervention is 1.2
R_0 from incubating only is 0.74

Consider the impact on the dynamics as the Diagnostic Effort is increased…


250
200
150
100
50
0
Mean duration
8
10
12
14
16
Time (yrs)


1
0.9
0.8
0.7
0.6
0.5
0.4
Prop diagnosed
8
10
12
14
16
Time (yrs)


Disease
Diagnosis
Death
Incidence /10,000 /Qtr
Time (yrs)
0
1
2
3
4
5
6
7
8
9
10
8
9
10
11
12
13
14
15
16

1. Decrease in Cases

- The lack of a large increase in cases as diagnostic effort increases is NOT indicative that IDM is not the sole cause of reduction in cases
- Increased IDM can reduce cases to very low levels, even though transmission remains endemic

2. Can IDM be improved?

- Early diagnosis is better
- Diagnosis of KA is hampered by poor diagnostics
  - >2wks fever + rK39 + splenomegaly
  - If IDM is key to control, then once all cases are diagnosed early, then IDM can only be improved by earlier diagnosis
- Time to diagnosis is a combination of health-seeking and diagnostic technology

Parasitology & Molecular tests

- **Parasitology**
  - Spleen – 95% sensitive
  - bone marrow – 60-85% sensitive
  - Specificity estimation 100% (Sundar 2002)

- **PCR**
  - **Sensitivity 92.3%** 95% CI: 88.4-94.9
  - **Specificity 63.3%** 95% CI: 53.9-71.8
  - Blood samples, consecutive studies international samples (Ruiter 2014 systematic review)

- All diagnostics only assessed for accuracy in symptomatic patients, including 14d fever. Relatively little is known about performance in asymptomatics.

Immunological Tests

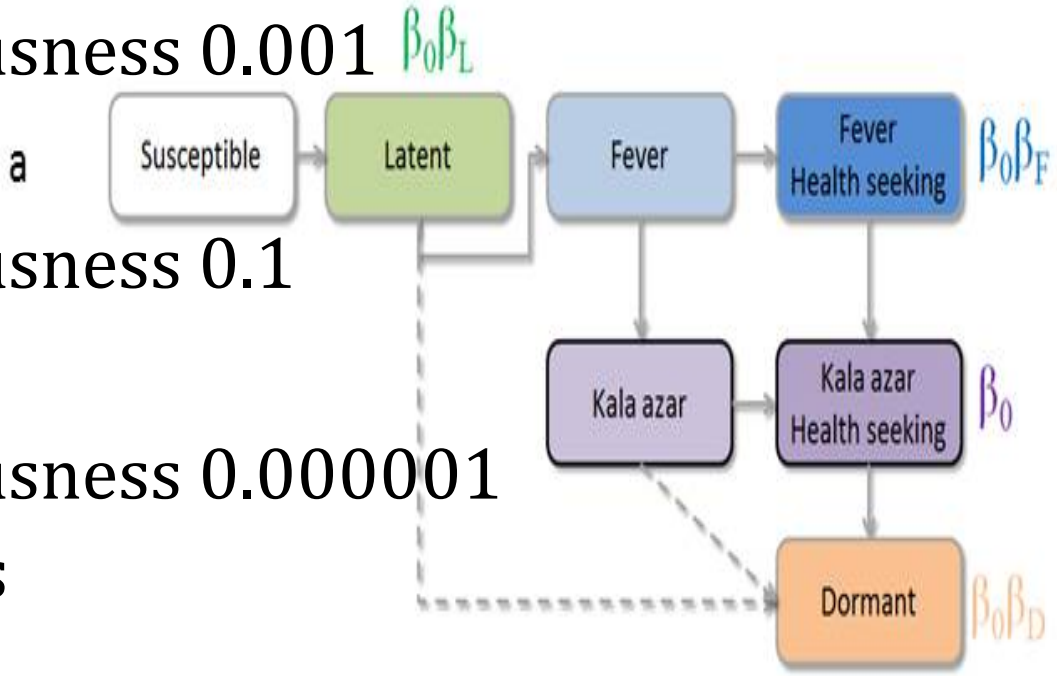
- **Serological (antibody detection) tests**
  - **rK39** tests used to identify patients for the elimination campaign
  - rK39 plus clinical symptoms now used as proxy for active infection – and treatment decision making
  - In ISC: **Sens: 97.0%** 95% CI: 90.0 to 99.5
  - **Spec: 90.2%** 95% CI: 76.1 to 97.7
  - Boelaert 2014 Cochrane systematic review – consecutive studies only
- **Direct Agglutination Test DAT**
  - Used as marker or incidence, exposure
  - In ISC: **Sens:** 97.1% 95% CI: 94.9 – 98.4
  - **Spec:** 95.7 95% CI: 88.1 – 98.5
  - Chappuis 2007 – systematic review
- **Leishmanin Skin Test LST**
- All diagnostics only assessed for accuracy in symptomatic patients. Relatively little is known about performance in asymptomatics.

Health-seeking and Health-care

- Retrospective assessment of path to diagnosis
- Shows distinct differences by locale
- Model with (one) biological process constant, and (two) behavioural processes different

Transmission Dynamic Model

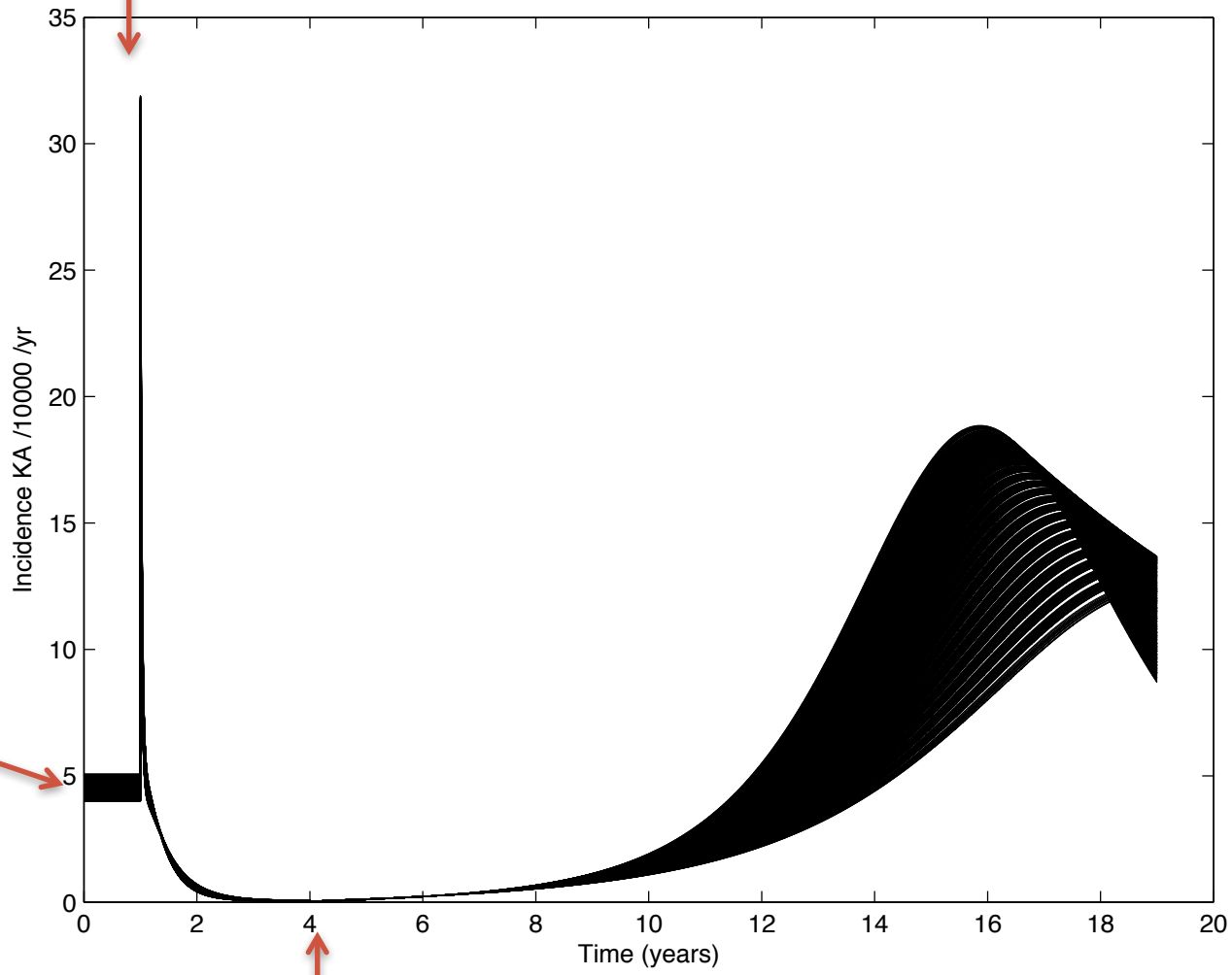
- Use this structure as the basis
- Latent (asymptomatic) infection
  - Duration 80d based on seasonality delays
  - Relative infectiousness 0.001
- Fever
  - Relative infectiousness 0.1
- Dormant
  - Relative infectiousness 0.000001
  - Reproduce cycles



Results

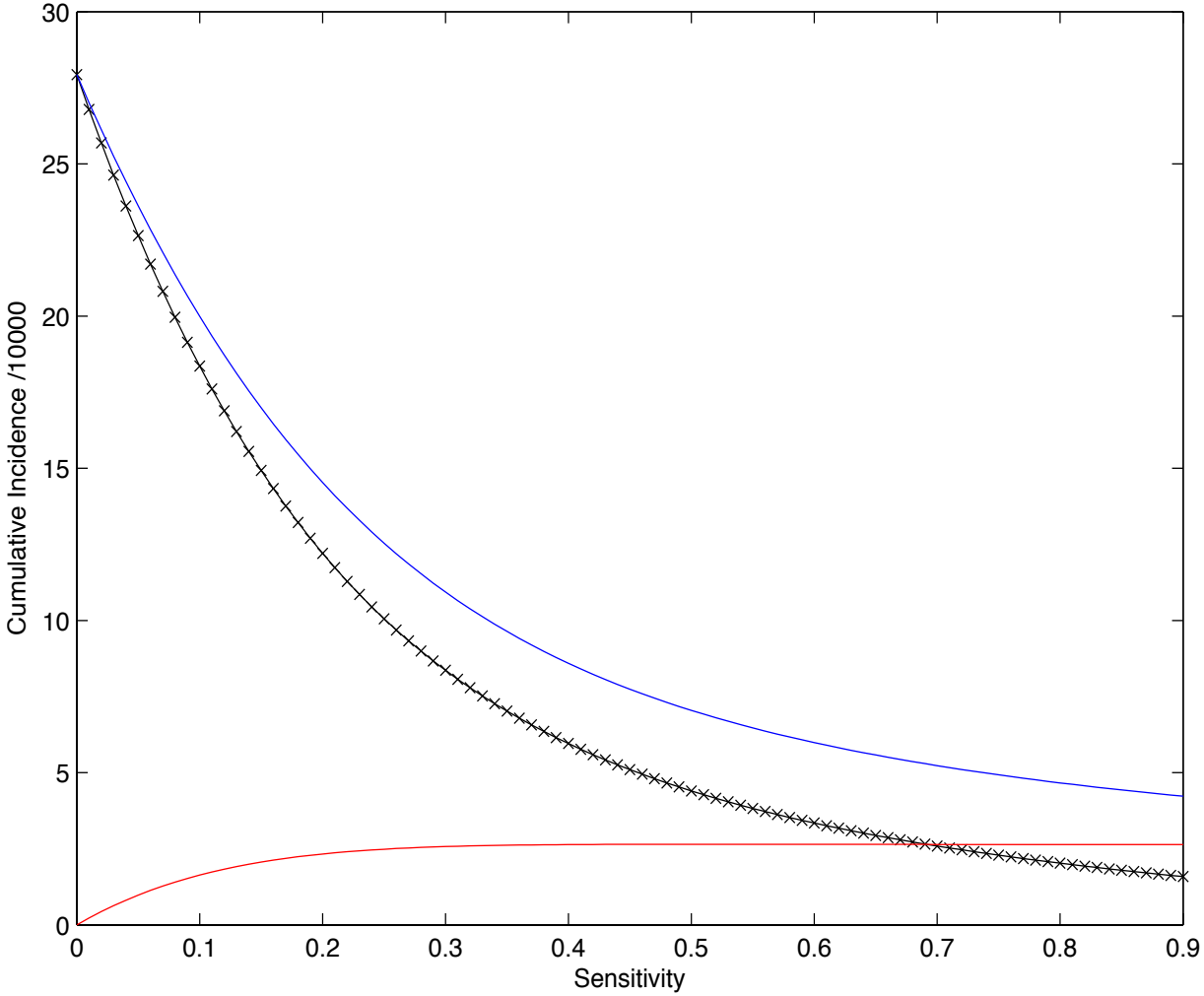
- What if we reduce diagnostic delays in Bihar?
  - Current pathways is attendance at private providers who fail to diagnose
  - Eventually diagnosed at government providers
  - Diagnostic pathways
- What sort of diagnostic profile is needed for a test prior to onset of clinical KA?
  - 14d fever is a barrier to early diagnosis & treatment

Reduce diagnostic delay to Nepal / Bangladesh:
spike in diagnoses & reduction in transmission



Endemic equilibrium state for Bihar

Return diagnostic delay to pre-intervention:
Slow return to pre-intervention + epidemic



Sum of the number of cases over 5 years post reduction in diagnostic delay

Marginal increases in sensitivity >30% are minimal

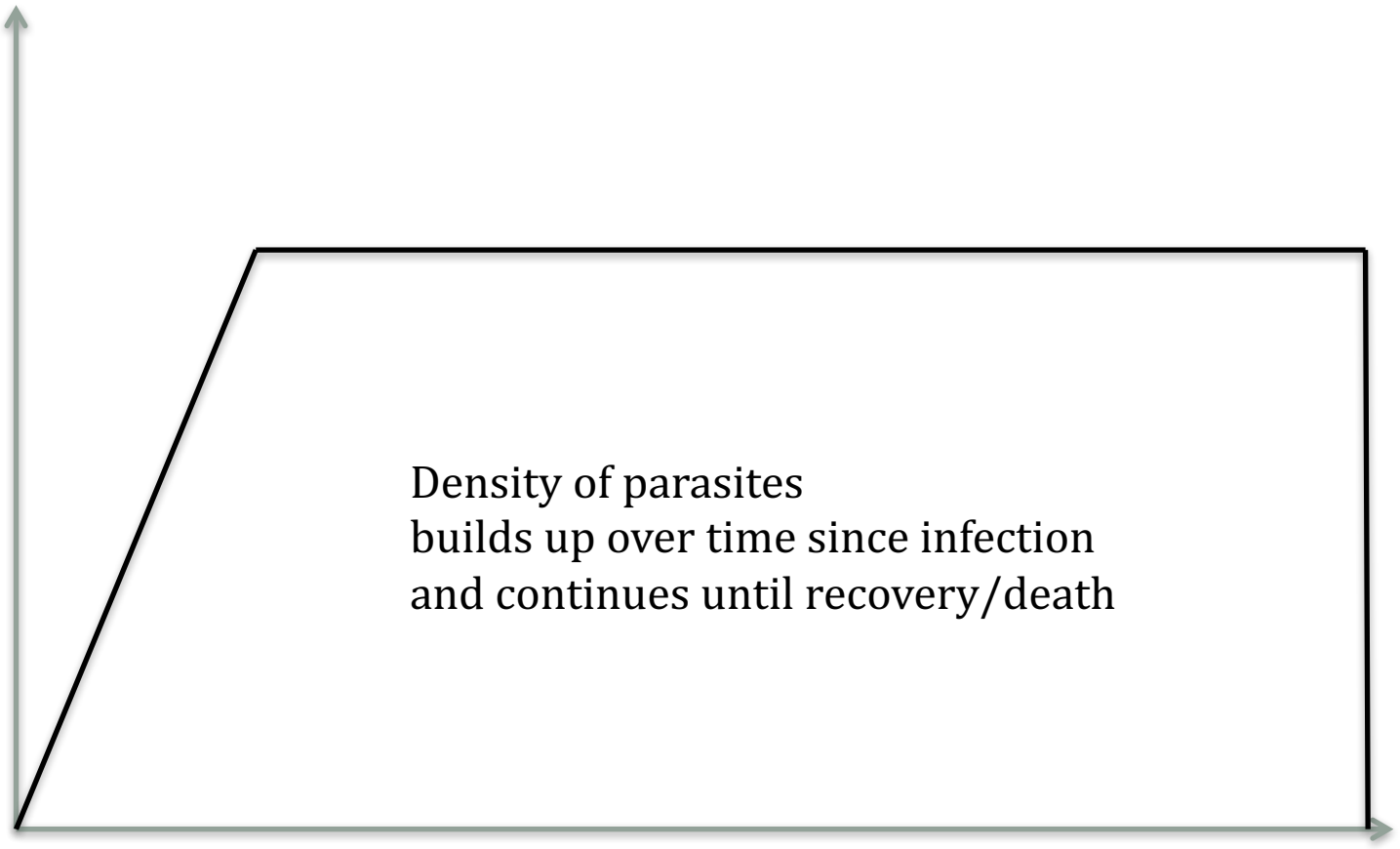
Pre-KA Diagnosis

- Active case finding
  - need not be a lab. diagnostic
- Shortens the infectious period
  - Can be highly efficacious even at relatively low sensitivity
  - E.g. preventing 50% of KA diagnoses reduces R_0 by ~1/2 depending on relative infectiousness and durations
- But diagnosis in individuals with low clinical suspicion is challenged by specificity
  - Even moderately low specificity prevents useable application
  - Currently available treatments for KA are too toxic to give to fever patients with a positive rK39 due to lack of specificity of the test without 2 weeks fever and a palpable spleen

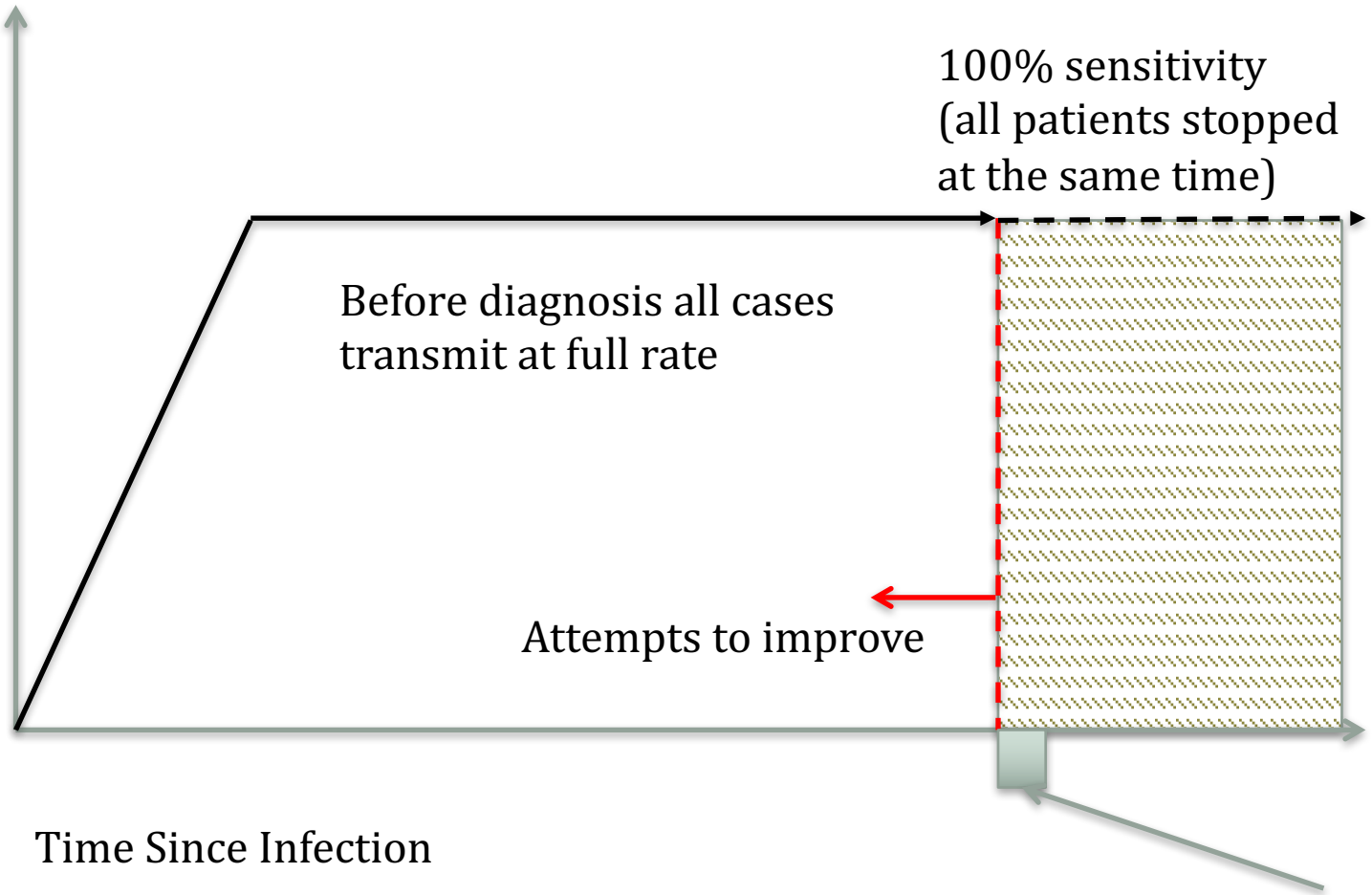
Testing Interval

- Realised sensitivity is a product of the rate of testing and the sensitivity per test
  - Assumes tests are independent
  - Population of health-seekers with fever are tested at a rate, with sensitivity & specificity at each test
- If each health-seeker with fever is tested once, then sensitivity is as exactly as presented
- All test realisations are products of testing accuracy and testing effort

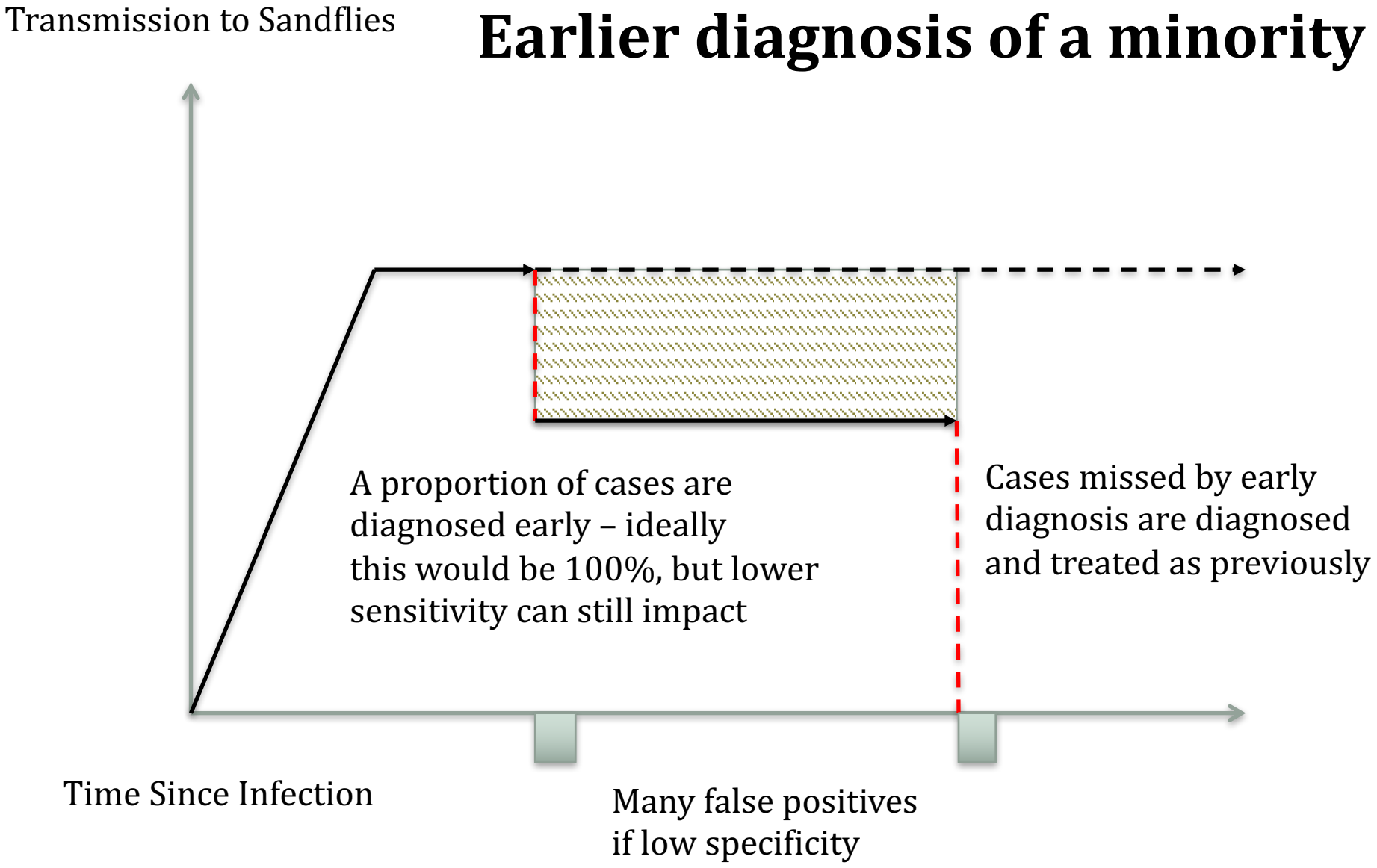
No Control

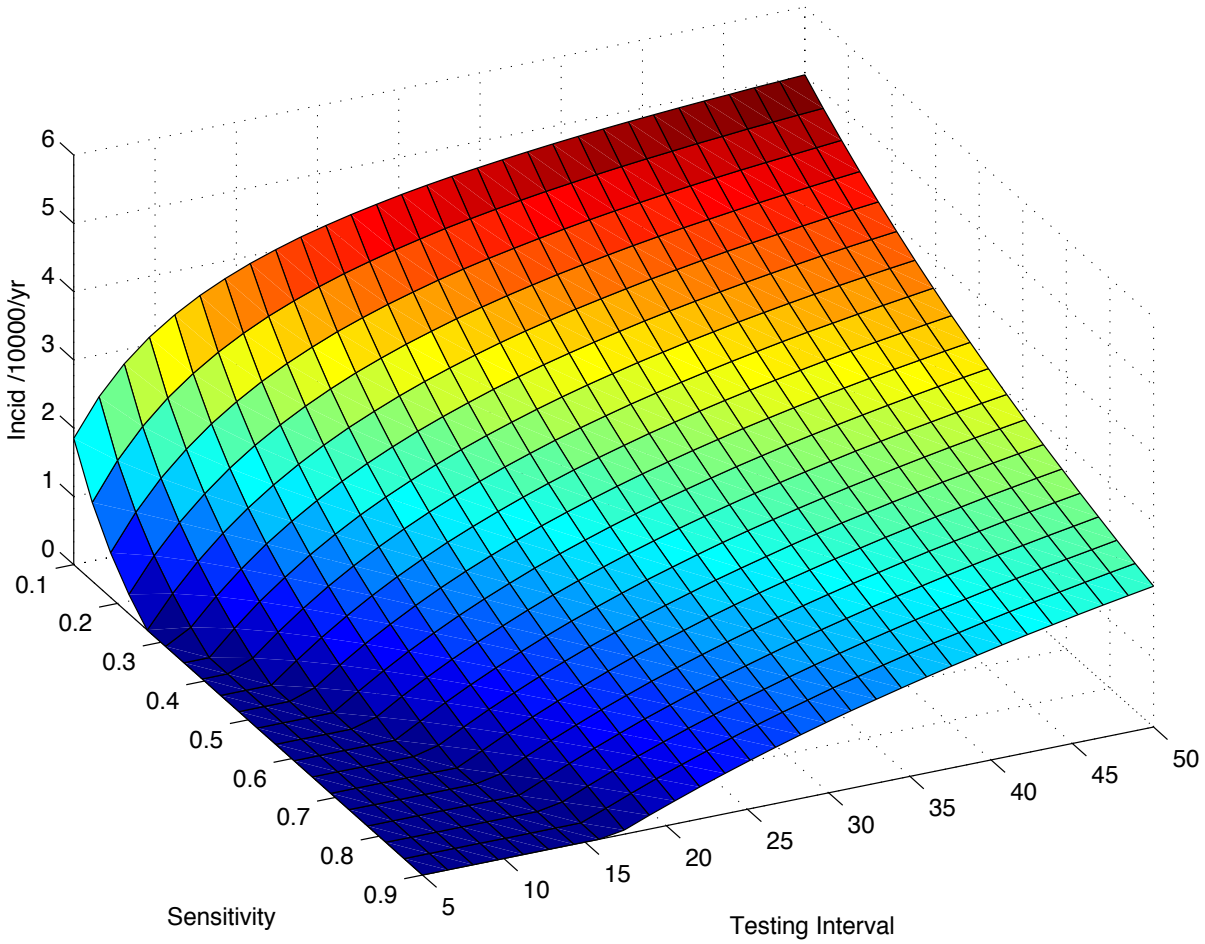

Transmission to Sandflies
Density of parasites
builds up over time since infection
and continues until recovery/death
Time Since Infection

Current Interventions

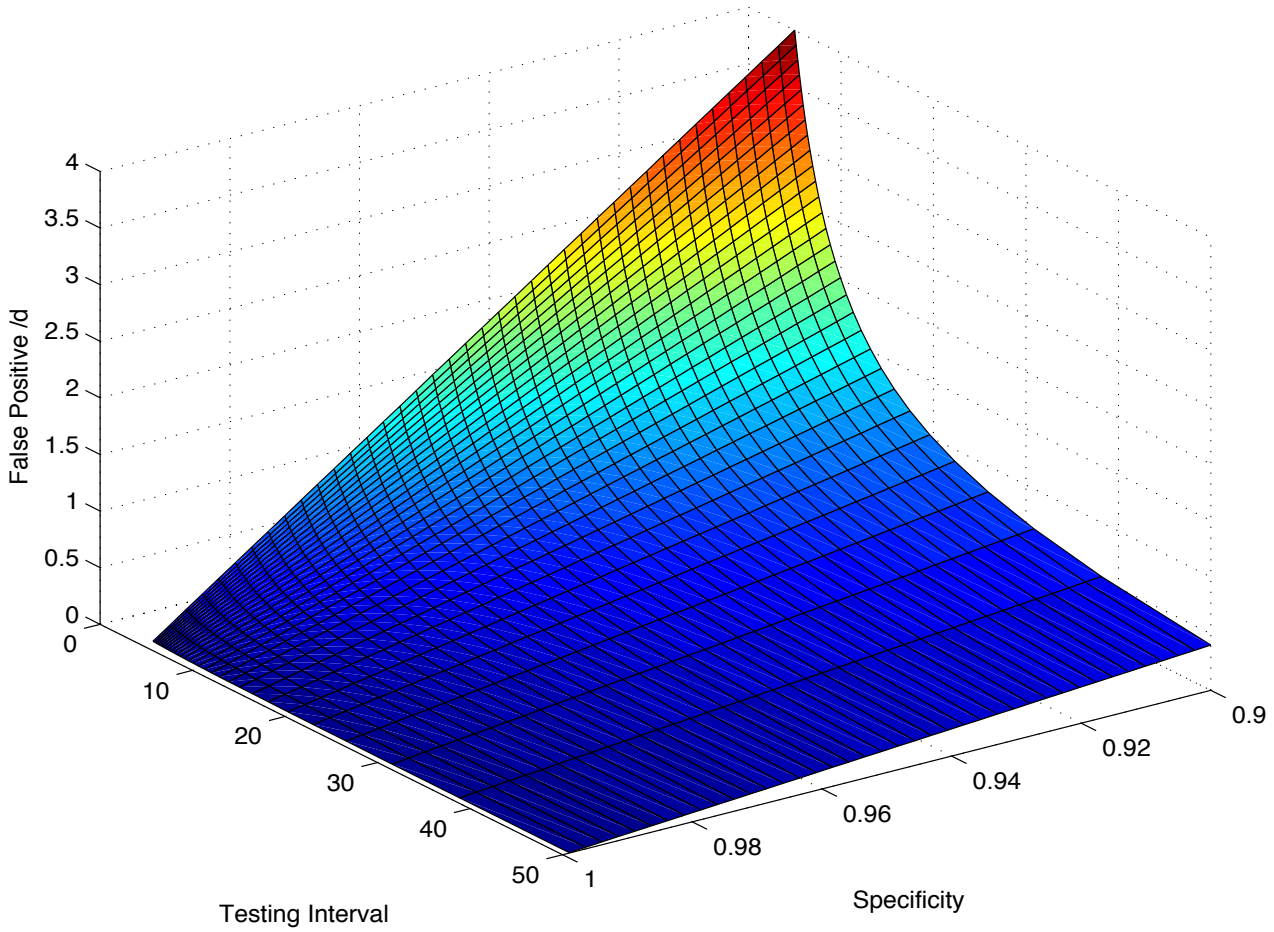


Earlier diagnosis of a minority



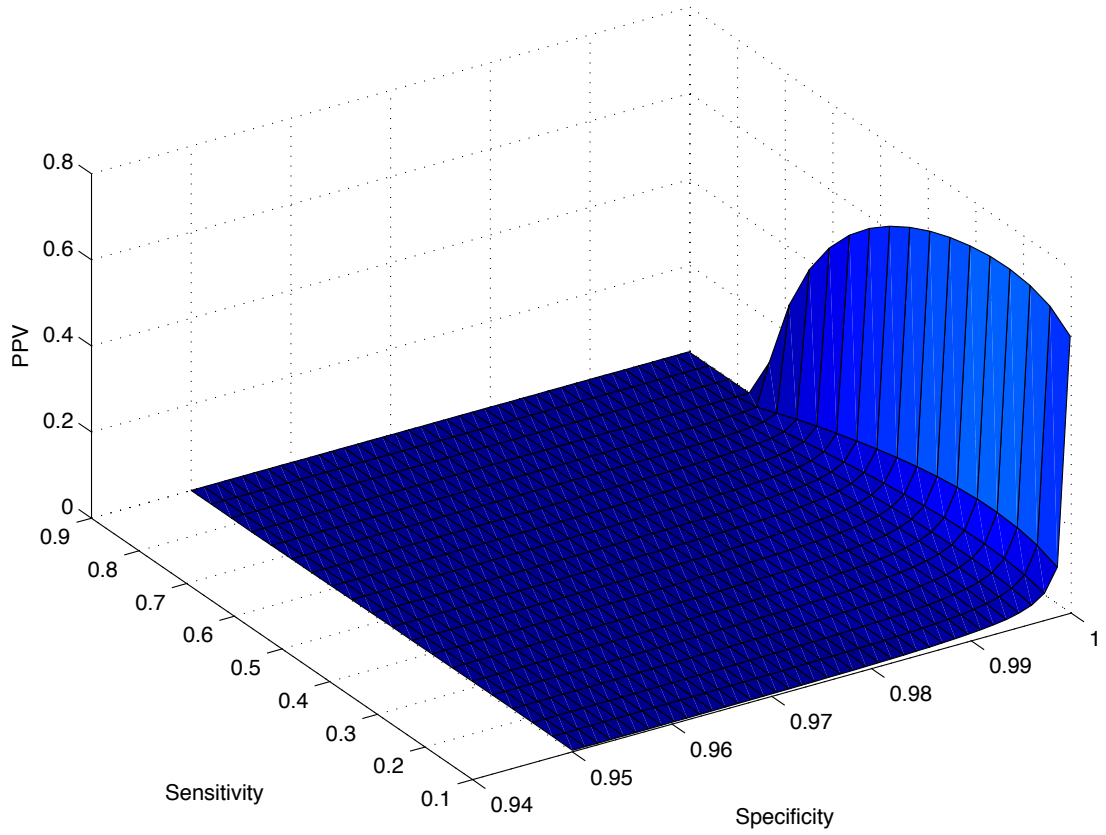


Equilibrium relationship between true per test sensitivity, testing frequency (the average time in days between tests) and the equilibrium incidence of KA /10000/yr (vertical). Testing frequency > 14d means that elimination is very difficult even with a good test (sensitivity >80%), but testing every 5-10days means that a test with only 40% sensitivity (on each test occasion) can eliminate.



Relationship between the testing interval and specificity on the number of false positives per day.

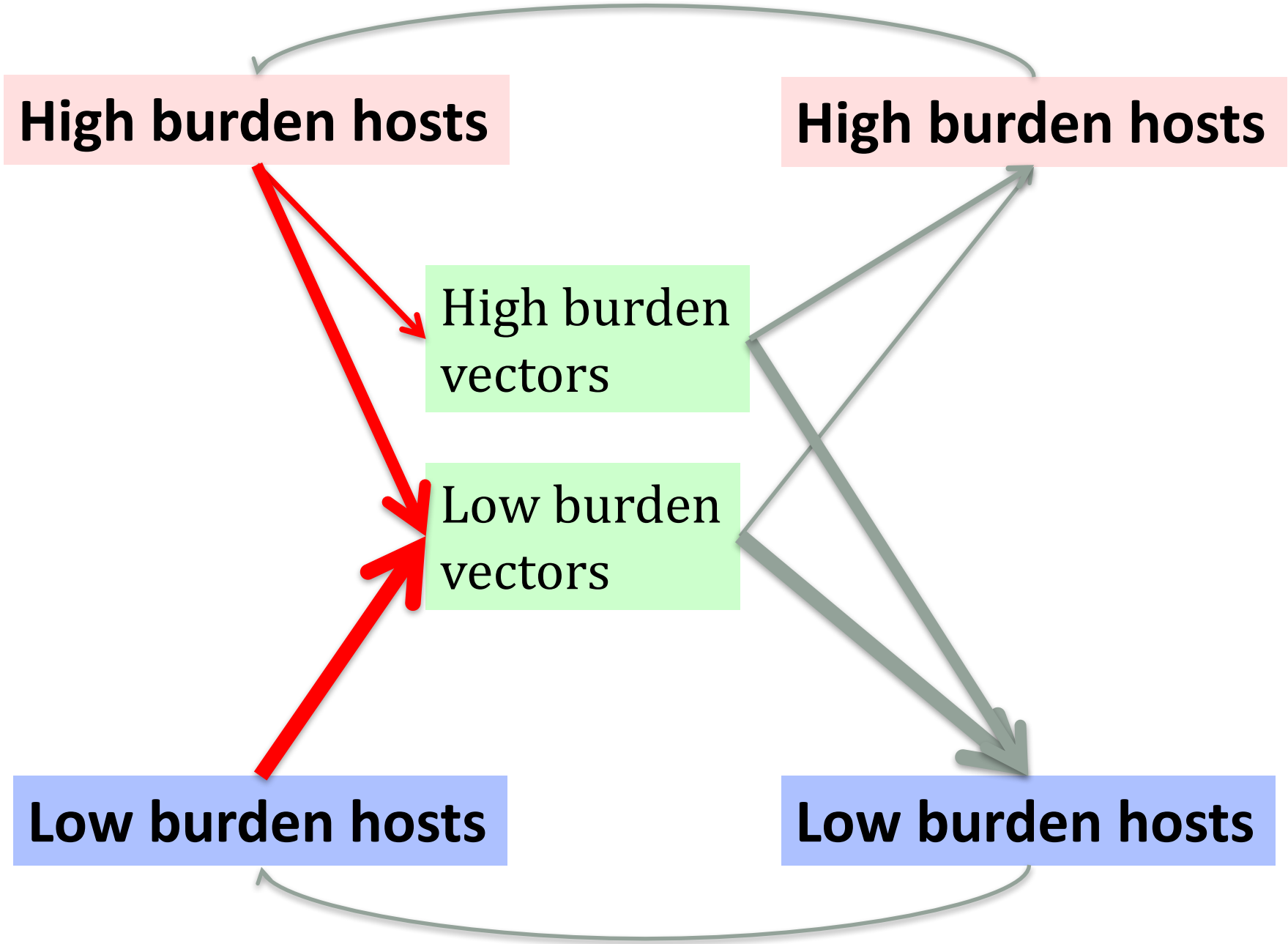
Assumes that there are 200 people (/10000) who have same clinical symptoms as Fh, so testing every 5 days gives 0.1*200/5 = 4 cases per day (90% specificity).



The positive predictive value (i.e. chance that a positive test is a true positive) for fixed testing interval (14d)
Note that as sensitivity increases and elimination is approached, all positives are false positives

3. Are we missing something?

- Dose of infection
  - To sandflies
    - From hosts with highest density of peripheral infection
    - Are these the most diseased hosts?
  - To hosts
    - From sandflies with heaviest burden
    - Are these hosts more likely to develop disease?
- Age at infection
  - Few child cases in the CARE data from Bihar
  - Are children less likely to develop disease, but equally as infectious (i.e. disease is immuno-pathology)


High burden hosts
High burden hosts
High burden vectors
Low burden vectors
Low burden hosts
Low burden hosts

VL Conclusions I.

- Differences in incidence between Nepal, Bangladesh and Bihar are entirely explainable by differences in diagnostic delays
  - Health-seeking might prevent prompt diagnosis – interactions between patient behaviour, health-care provision and disease processes
- Shortening diagnostic delays has great impact
  - Resurgent epidemics prevented by maintaining clinical vigilance and short diagnosis times
- If KA cases are not most infectious, then IRS has been the most important intervention

VL Conclusions II.

- Diagnosis before onset of specific clinical symptoms can have a large impact
  - Relatively low sensitivity (<50%) can eliminate
  - But will create large numbers of false positives if specificity is <99%
  - Current technologies (PCR, are close to requirements), but not being implemented because sensitivity is too low

VL Conclusions III.

- Dynamic pattern is consistent with increased diagnostic effort reducing transmission
  - Even if it will not curtain transmission
- Need to add spatial aspects to this
  - KA cases are highly clustered

SPEAK India

Setting the Post-Elimination Agenda for Kala-azar in India

BILL & MELINDA GATES foundation

NTD MODELLING CONSORTIUM

Mary Cameron

Simon Croft

Shannon McIntyre

Deirdre Hollingsworth

Piero Olliaro

Emily Adams

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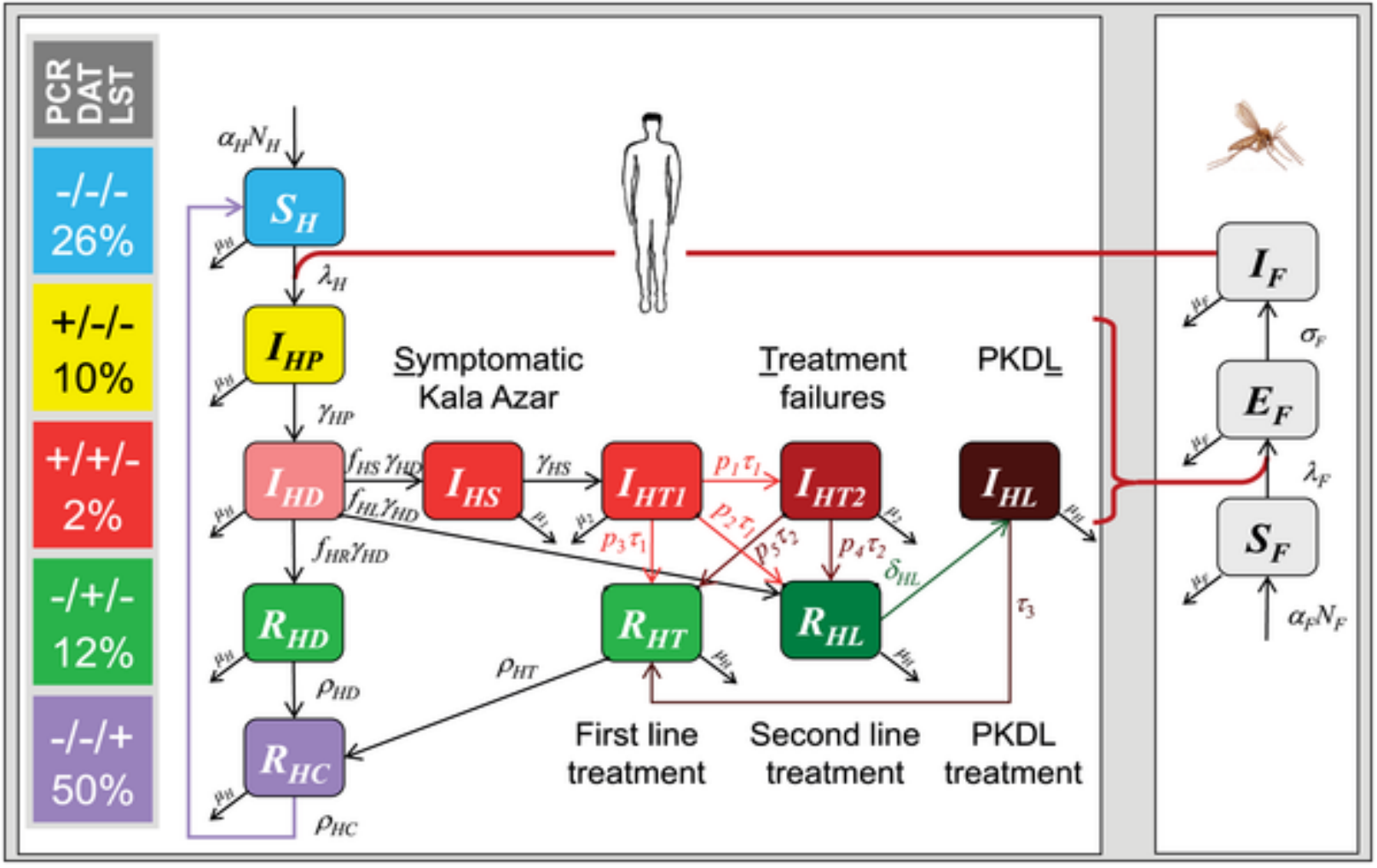
Recent VL Modelling Publications

- **Le Rutte EA *et al*. Feasibility of eliminating visceral leishmaniasis from the Indian subcontinent: explorations with a set of deterministic age-structured transmission models. Parasit Vectors**
- Chapman LAC *et al.* Quantification of the natural history of VL and consequences for control. *Parasites & Vectors* 2015; **8**:521.
- **Medley GF, Hollingsworth TD, Olliaro PL, Adams ER. Health-seeking behaviour, diagnostics and transmission dynamics in the control of visceral leishmaniasis in the Indian subcontinent. *Nature* 2015; 528:S102–S108.**
- Rock, K.S. *et al*. (2015) Uniting mathematics and biology for control of visceral leishmaniasis. *Trends Parasitol.* **31,** 251–259 (2015).
- Cameron, M.M. *et al*. (2016) Understanding the transmission dynamics of *Leishmania donovani* to provide robust evidence for interventions to eliminate visceral leishmaniasis in Bihar, India. *Parasites & Vectors* (2016) 9:25

Figure 1. Model for L. donovani infection, transmission and control.



Stauch A, Sarkar RR, Picado A, Ostyn B, et al. (2011) Visceral Leishmaniasis in the Indian Subcontinent: Modelling Epidemiology and Control. PLoS Negl Trop Dis 5(11): e1405. doi:10.1371/journal.pntd.0001405
http://www.plosntd.org/article/info:doi/10.1371/journal.pntd.0001405

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