Prevalence of Malaria Attributable Fever: Definition, Inference and Sensitivity Analysis

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Rubin Causal Model (RCM): Personal Experiences

- Dissertation on instrumental variables (IV)
  - Only knew about simultaneous equations econometric framework for most of working on dissertation.
  - When writing literature review, found Holland (1986)'s exposition of RCM and Angrist, Imbens and Rubin (1996).
  - Illuminated what can be learned from IVs.
- Got interested in malaria.
  - Malaria attributable fraction. Defined in terms of observables. Science? Assignment Mechanism? Assumptions?

Malaria Background

- Malaria: Disease caused by a parasite that lives part of its life in humans and part in mosquitoes.
- Major public health problem in children in sub-Saharan Africa.
- A main symptom of malaria is fever.

Malaria Attributable Fever

- Malaria Attributable Fraction (MAF): Proportion of fevers among children in a given area that are “attributable to”, i.e., “caused by,” malaria.
- MAF is important for
  - Planning sample size of clinical trial.
  - MAF|Symptoms important for decision to treat with antimalarials.
- Prevalence of Malaria Attributable Fever (PMAF): MAF*prevalence of fevers
  - Understanding how burden of malaria is changed by interventions.
  - Prioritizing resources: public health burden of malaria vs. other diseases

Potential Outcomes

d : malaria parasite density

z : non-malaria infection level (0 = no non-malaria infections)

$Y_i^{(d,z)}$: potential fever outcome for child *i* if malaria parasite density set to *d* and non-malaria infection level to *z*

D_i, Z_i : realized parasite density, non-malaria infection for *i*

$Y_i^{obs} = Y_i^{(D_i, Z_i)}$: observed outcome

$Y_i^{nmi} = Y_i^{(0, Z_i)}$: potential outcome under an intervention that eliminates malaria parasites from the body

Malaria attributable fever: fever that would not have occurred if child had been given intervention that would prevent child from having malaria parasites

Defining the MAF

Malaria attributable fraction (MAF): Fraction of fevers that are attributable to malaria, $P(Y^{nmi} = 0 \mid Y^{obs} = 1)$

MAF depends on intervention.

No side effects assumption: Intervention cannot cause a fever.

$P(Y^{nmi} = 1, Y^{obs} = 0) = 0$.

Under no side effects, MAF is proportion of fevers that would be eliminated if malaria was eradicated without side effects.

We wouldn't specify the intervention but assume it satisfies no side effects assumption.

MAF provides measure of *potential* benefit of eliminating malaria.

- Useful to policymakers (Walter, 1976, Biometrics).

Estimating the MAF

MAF= $P(Y^{nmi} = 0 \mid Y^{obs} = 1)$

MAF could be estimated from a survey by a usual ratio estimator if it was easy to determine whether a fever $(Y^{obs} = 1)$ was attributable to malaria parasites ($Y^{nmi} = 0$).

Problem: There's no gold standard way to determine whether a fever was attributable to malaria parasites.

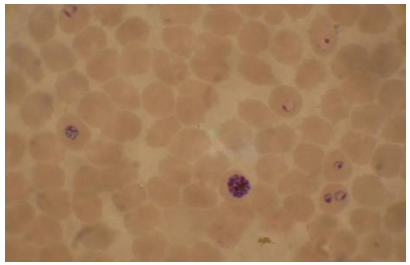
Challenges in Estimating MAF

- Hard to diagnose that a fever is being caused by malaria parasites.
  - Fevers and other health problems caused by clinical malaria are similar to those of influenza, pneumonia, viral hepatitis or typhoid fever.
  - Study in Mali in 1991: Only 54% of cases diagnosed as malaria actually had malaria parasites in blood.
- Improved way to diagnose fever as being attributable to malaria: microscopic examination of the blood.

Microscopic Blood Examination for Malaria Parasites

- Blood film (thick film) examination:
  - Take drops of blood from patient, spread onto a slide to make a thick film and allow to dry.
  - Apply a differential stain (Giemsa stain).

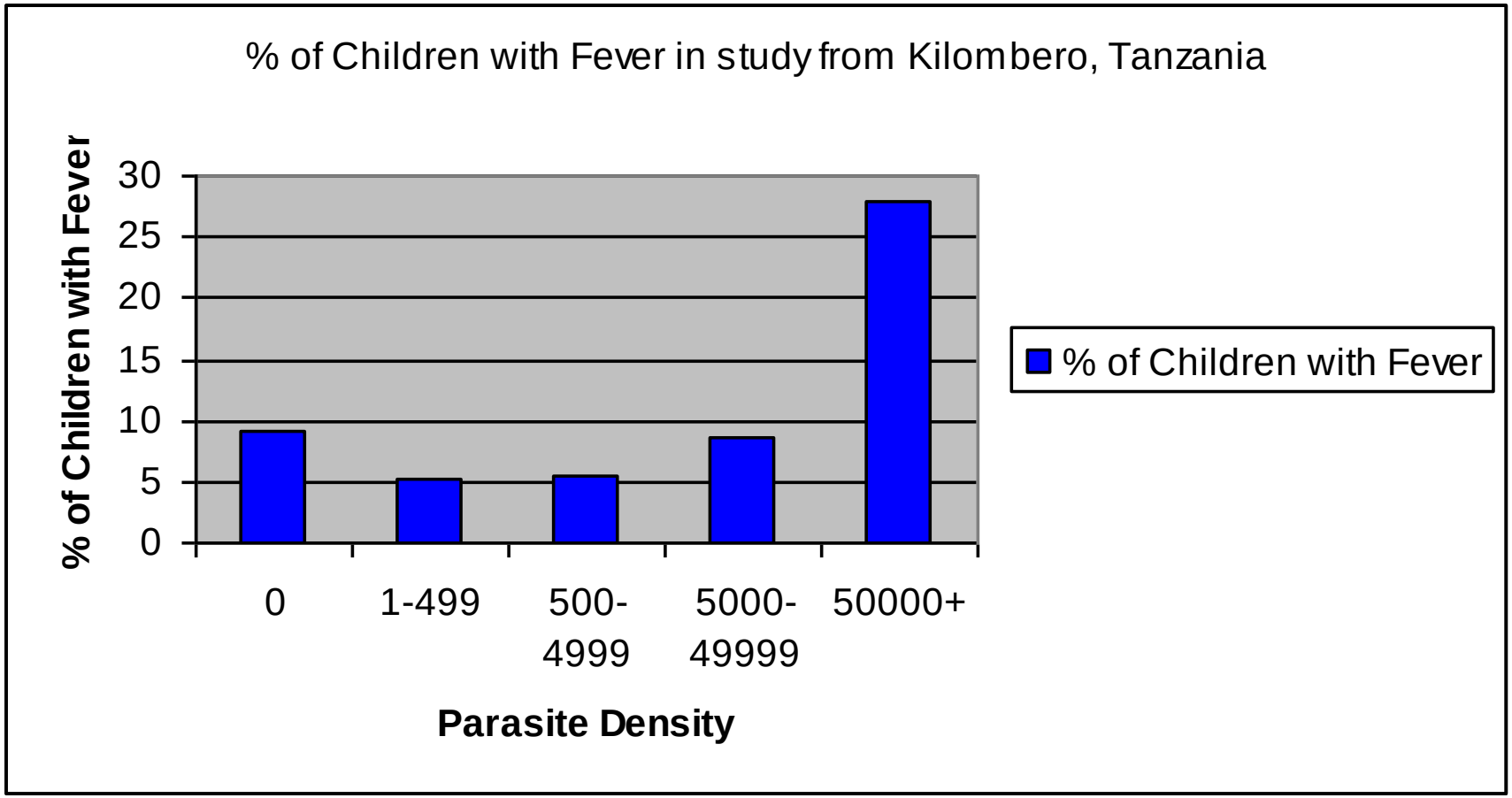
    The stain dissolves the contents of red blood cells. What remains are the remnants of red blood cells, white blood cells, platelets, parasites and bacteria.
  - Use light microscope to examine the film.



- Measure parasites/µl of blood. Count parasites per white blood cell and assume a constant number of white blood cells per µl (8000).

Kilombero Malaria Project

Cross-sectional study. 6.9% of children had fever.



Source: Smith et al., 1994

Parasite Density and Malaria Attributable Fever

- Presence of fever and parasites does not prove malaria is causing the fever because
  1. Other infections may be sufficient causes of the fever.
  2. Pyrogenic Threshold – a minimum parasite density is needed in order for fever to occur. Varies from individual to individual, with partial immunity increasing the parasite density.
- Children living in malarious areas often tolerate substantial malaria parasites without developing any illness due to partial immunity:
  - Innate resistance to malaria.

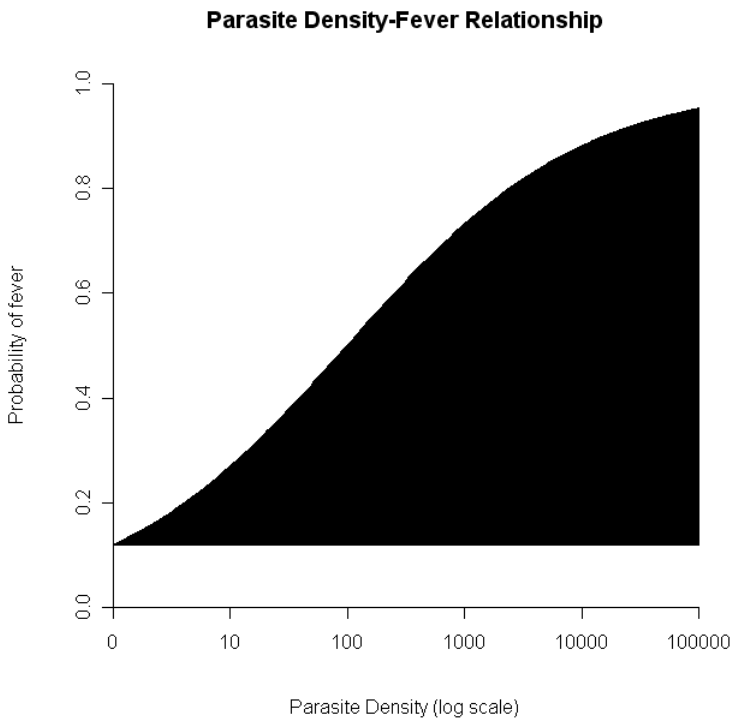
    Example: Sickle cell trait.
  - Acquired immunity to malaria.
- Summary: There is no foolproof way to detect a fever as being caused by malaria parasites, but the higher the density of the parasites, the more likely the fever is to be due to the parasites.

Classical Attributable Fraction Estimation

$$\hat{MAF} = \frac{1}{\sum Y_i^{obs}} \sum_{i:Y_i^{obs}=1} \hat{P}[Y^{nmi} = 0 \mid Y^{obs} = 1, D = D_i] =$$

$$\frac{1}{\sum Y_i^{obs}} \sum_{i:Y_i^{obs}=1} \frac{\hat{P}[Y^{obs} = 1 \mid D = D_i] - \hat{P}[Y^{obs} = 1 \mid D = 0]}{\hat{P}[Y^{obs} = 1 \mid D = D_i]}$$

where $\hat{P}(Y^{obs} = 1 \mid D)$ could be estimated via logistic regression or a more nonparametric method.



Example:

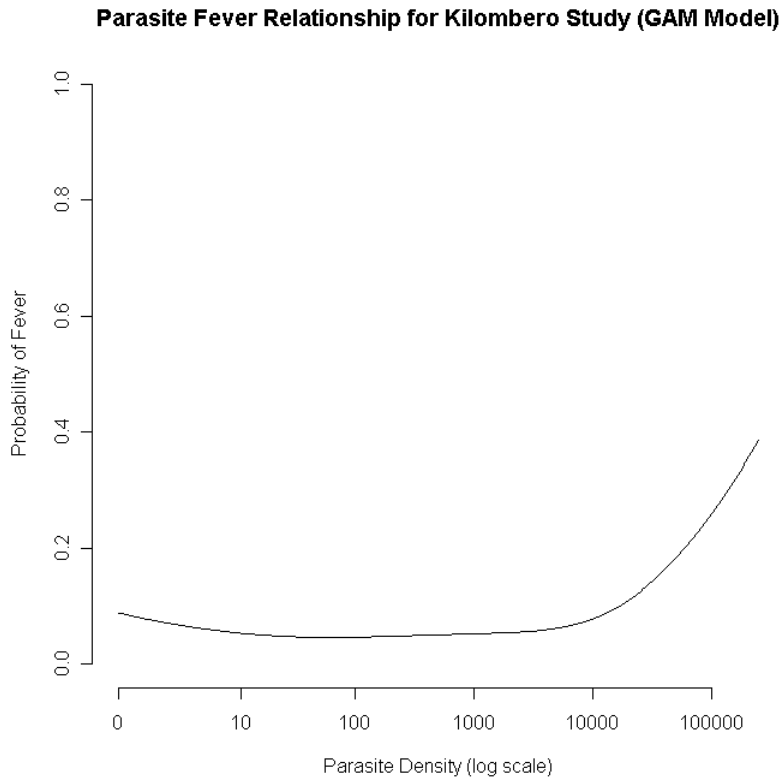
Y^{obs}	D	Number
0	0	425
0	1000	125
1	0	75
1	1000	375

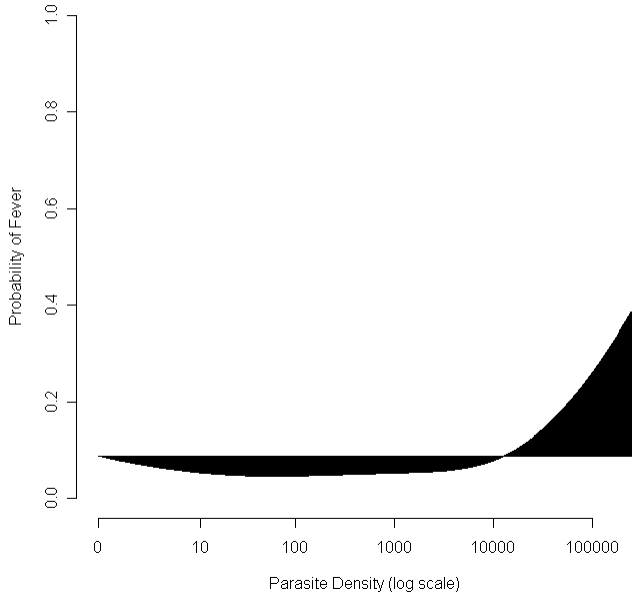
$$\hat{MAF} = \frac{1}{1000}\left(\begin{array}{l} 75 * \frac{(75/500) - (75/500)}{75/500} + \\ 375 * \frac{(375/500) - (75/500)}{375/500} \end{array}\right) = 0.30$$

Classical Estimate for Kilombero Project

$$\hat{MAF} = 0.18$$

95% CI: (0.14, 0.22)





Assumptions for Classical Estimate to be Consistent

A1. No side effects of intervention assumption

$$P(Y^{nmi} = 1, Y^{obs} = 0) = 0$$

A2. Let D^{obs} denote the measured parasite density and D^{cur} true density.
If a fever is malaria attributable, then the measured parasite density is greater than 0.

A3. The measurement error in parasite density, $D^{obs} - D^{cur}$, is independent of whether child has non-malarial fever causing infection which is represented by Y^{nmi}.

A4. The true current parasite density D^{cur} is independent of non-malarial fever causing infections Y^{nmi} conditional on measured covariates X (true current parasite densities are effectively random assigned conditional on X).

Reasons Why A2 Might Be Violated

A2. If a fever is malaria attributable, then the measured parasite density is >0.

1. Sample variability. The parasite density is estimated from a sample of blood.
2. Loss of parasites in sample handling and staining process.
3. Microscopy error. Accuracy of parasite density measurement depends on quality of microscopist.
4. Sequestration and synchronization. Microscopic examination only estimates parasite density in peripheral blood.

Reason Why A3 Might Be Violated

A3. The measurement error in parasite density, $D^{obs} - D^{cur}$, is independent of whether child has non-malarial fever causing infection which is represented by Y^{nmi}.

- The most common method of estimating parasite density counts the number of parasites found for a fixed number of white blood cells and then assumes there are 8000 white blood cells per μl of blood.
- White blood cell counts actually vary considerably from person to person and in particular can be altered by an infection such as influenza.

Reasons Why A4 Might Be Violated

A4. The true current parasite density D^{cur} is independent of non-malarial fever causing infections Y^{nmi} conditional on measured covariates $\boldsymbol{X}$ (true current parasite densities are effectively random assigned conditional on $\boldsymbol{X}$).

1. Unobserved confounders such as sanitary conditions.
2. Fever due to non-malaria infection kills parasites.

Evidence for Parasites Being Killed by Fever and Consequences

- In vitro evidence: High temperatures have been found to inhibit malaria parasites growth in cultures (Kwiatkowski, 1989, Journ. of Exp. Med.; Long *et al*., 2000, Paras. Res.)
- In vivo evidence: Malaria parasite density has been found to be suppressed during febrile illnesses measles and influenza (Rooth and Bjorkman, 1992, Am. J. Tr. Med. & Hyg.).
- Consequence of parasites being killed by fever: Children with non-malaria fever-causing infections (Y^{nmi}=1) have lower true current parasite density (D^{cur}) on average than children without non-malaria fever-causing infections (Y^{nmi}=0).

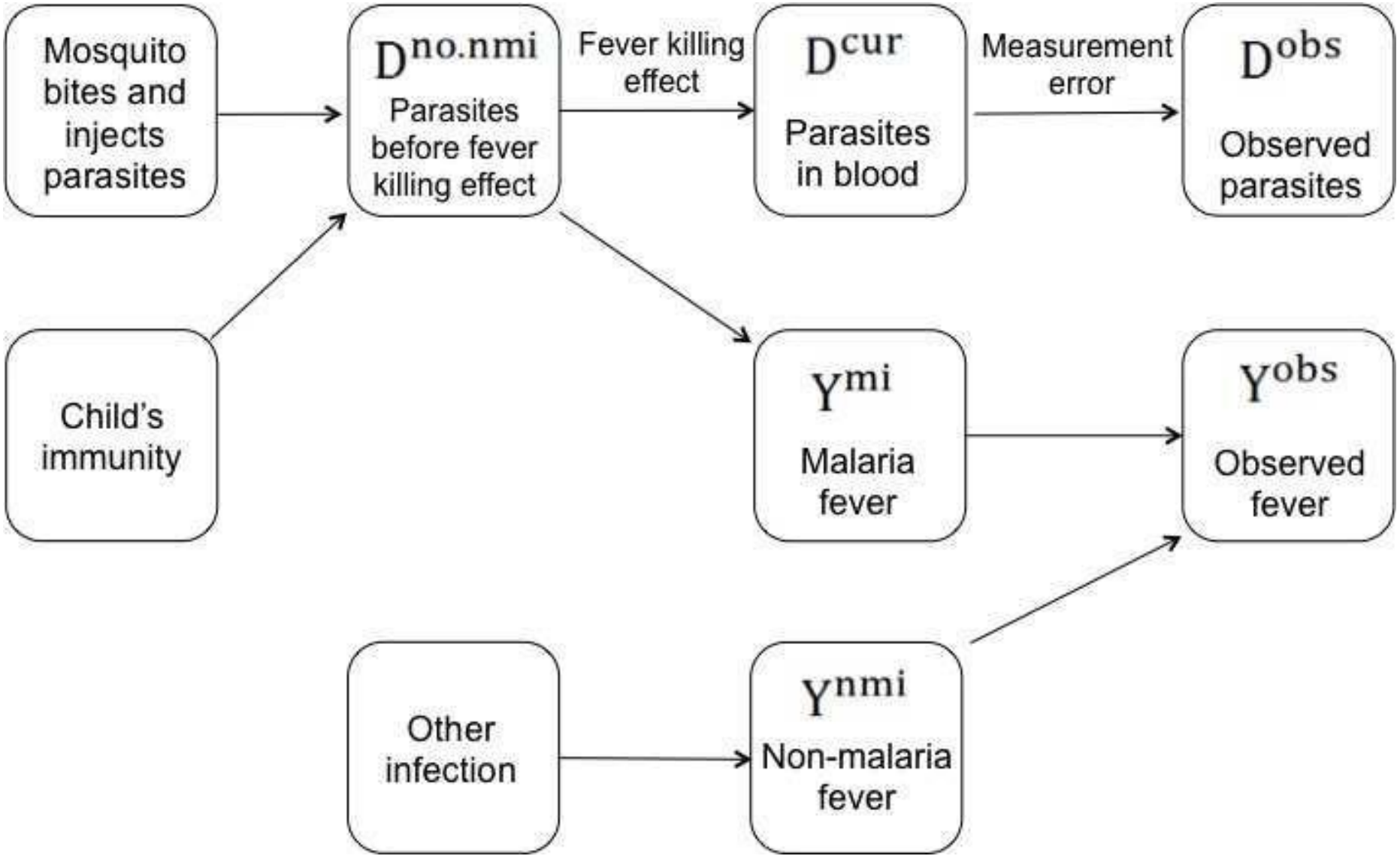
Simulation: Classical Method

True MAF is 0.5.

	Model for $P(Y^{obs} \mid D^{obs})$		
	Logistic Regression	Logistic Regression with Power Parameter	Local Nonparametric Regression with Isotonic Smoothing
No fever killing, no measurement error	0.449	0.470	0.507
No fever killing, measurement error	0.442	0.386	0.476
Fever killing, measurement error	0.286	0.258	0.370

Summary: Classical method can be substantially biased under fever killing and measurement error in parasite density.

Goal: Develop sensitivity analysis method for fever killing and measurement error.


Mosquito bites and injects parasites
$D^{no.nmi}$
Parasites before fever killing effect
Fever killing effect
D^{cur}
Parasites in blood
Measurement error
D^{obs}
Observed parasites
Child's immunity
Y^{mi}
Malaria fever
Y^{obs}
Observed fever
Other infection
Y^{nmi}
Non-malaria fever

Sensitivity Analysis for Fever Killing and Measurement Error

Sensitivity analysis parameters: β , density f

Fever killing: Fever kills $(1-\beta)$ of the parasites.

Measurement error mechanism:

$D_i^{obs} \mid D_i^{cur} \sim f(x; D_i^{cur})$,

e.g., Poisson(D_i^{cur})

Negative Binomial $(6, 6+D^{cur})$ based on data from O'Meara et al. (2007).

Bayes Deconvolution Problem

Split observed data into febrile $(Y^{obs} = 1)$ and afebrile $(Y^{obs} = 0)$ components and model parasite densities for each component.

$$D^{no.nmi} \mid Y^{mi} = 0 \sim g_1$$

$$D^{no.nmi} \mid Y^{mi} = 1 \sim g_2$$

$$g_2(0) = 0 \ .$$

Assumption: Y^{mi} independent of Y^{nmi}.

Relaxed in further sensitivity analysis.

$$\lambda^* = P(Y^{mi} = 1 \mid Y^{obs} = 1)$$

$$D^{no.nmi} \mid Y^{obs} = 0 \sim g_1$$

$$D^{no.nmi} \mid Y^{obs} = 1 \sim (1 - \lambda^*) g_1 + \lambda^* g_2$$

Bayes Deconvolution Problem

Considering fever killing,

$$D^{no.nmi} \mid Y^{obs} = 0 \sim g_1$$

$$D^{no.nmi} \mid Y^{obs} = 1 \sim (1-\lambda^*) g_1^* + \lambda^* g_2$$

$$g_1^*(x) = g_1(x/\beta)$$

Using measurement error mechanism *f*

$$D^{obs} \mid Y^{obs} = 0 \sim f \circ g_1$$

$$D^{obs} \mid Y^{obs} = 1 \sim (1-\lambda^*) f \circ g_1^* + (\lambda^*) f \circ g_2$$

Bayes deconvolution problem.

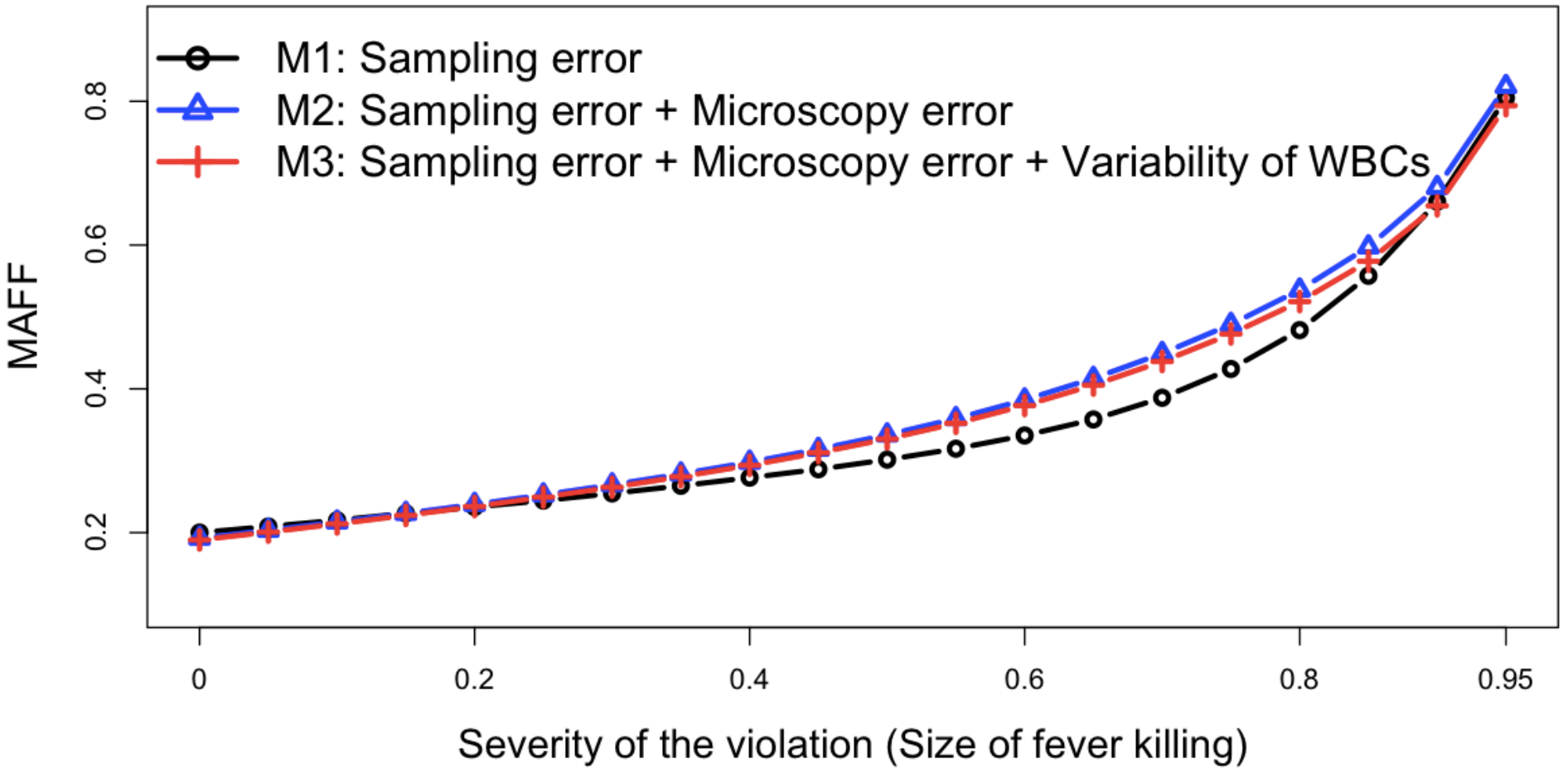
Following Efron (2016), we consider flexible exponential family models for g_1 (and hence g_1^*) and g_2, and maximize the likelihood.

True MAF is 0.5.
Regular = Exponential family approach without penalization
Penalized = Exponential family approach with penalized
Parametric, Nonparametric = Classic approach
Semiparametric = Semiparametric approach proposed by Vountasou and Smith and Qin and Leung.

			MAFF				
n	$Exp?$	β	Regular	Penalized	Parametric	Semi-	Non-
500	Yes	1	0.50 (0.12)	0.49 (0.12)	0.44 (0.09)	0.47 (0.08)	0.48 (0.08)
		0.8	0.50 (0.12)	0.49 (0.11)	0.41 (0.10)	0.44 (0.09)	0.44 (0.08)
		0.2	0.51 (0.06)	0.49 (0.05)	0.12 (0.04)	0.14 (0.06)	0.14 (0.06)
1000	Yes	1	0.50 (0.08)	0.49 (0.08)	0.44 (0.06)	0.47 (0.06)	0.47 (0.06)
		0.8	0.50 (0.08)	0.49 (0.07)	0.41 (0.07)	0.44 (0.06)	0.44 (0.06)
		0.2	0.51 (0.04)	0.50 (0.03)	0.12 (0.02)	0.14 (0.04)	0.14 (0.04)
500	No	1	0.49 (0.12)	0.50 (0.13)	0.42 (0.09)	0.46 (0.09)	0.47 (0.08)
		0.8	0.49 (0.11)	0.50 (0.12)	0.38 (0.10)	0.42 (0.09)	0.43 (0.08)
		0.2	0.51 (0.06)	0.51 (0.07)	0.12 (0.03)	0.13 (0.06)	0.14 (0.06)
1000	No	1	0.50 (0.09)	0.50 (0.10)	0.42 (0.07)	0.45 (0.06)	0.46 (0.06)
		0.8	0.50 (0.09)	0.50 (0.09)	0.38 (0.07)	0.42 (0.06)	0.43 (0.06)
		0.2	0.50 (0.05)	0.49 (0.04)	0.13 (0.02)	0.14 (0.04)	0.14 (0.04)

For every fever killing effect size, our proposed method produced unbiased estimates while the existing methods didn't

Application to Kilombero Data



Application in Progress to Cerebral Malaria (CM)

- Similar issues arise in estimating proportion of WHO defined CM due to malaria parasites.
- WHO defines CM as altered state of consciousness, infection with malaria parasites and no other identified cause of altered state of consciousness.
- WHO definition lacks specificity – signs of cerebral malaria are non-specific and many children in malaria endemic areas develop immunity so that they can tolerate parasites.
- Autopsy study: Taylor et al. (2004) found that 23% of children diagnosed with CM had known other cause of death (e.g., bacterial sepsis, viral infections).

Sample Size for Clinical Trial

- Planning clinical trial with Karl Seydel and Terrie Taylor of new drug regimen for treating cerebral malaria.

- For power calculations, we want to know the proportion of WHO defined CM that is attributable to malaria parasites.

Summary

- We used RCM to define MAF.
- Classical methods of estimating the MAF are biased by fever killing and measurement error.
- We developed sensitivity analysis.
- Further research into magnitude of fever killing and measurement error mechanisms would narrow range for plausible values of sensitivity parameters.
- Paper by K. Lee and D. Small on ArXiv: https://arxiv.org/pdf/1605.07663.pdf
- Thanks!