An Econometric Method for Estimating Population Parameters from Non-Random Samples: An Application to Clinical Case Finding

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Motivation

How are MDR-TB prevalence rates currently determined?

- Surveillance study
  - Accurate but infrequent
- Notification rates
  - Number of reported cases likely underestimate
- WHO crude adjustment to notification rates
  - Based on expert opinion (Glaziou et al. 2015)

Our contribution

- Develop a new econometric method for estimating population means from a selected sample
  - Identifies under-detection
  - Minimal data requirements: routine data
  - Minimal assumptions
  - Low cost, easy real-world implementation
- Useful for monitoring rare and emerging diseases
- We estimate that 16 to 26 % of all multi-drug resistant TB cases in South Africa were undiagnosed 2004-2011

Foundation for method

- Methods to address sample selection on unobserved characteristics in economics literature
  - Instrumental variables (see Imbens and Angrist 1994, Angrist and Imbens 1995)
  - Bivariate normal style selection models (see Heckman 1976)
- HIV lit: adjusting survey estimates for representativeness
  - Interviewer random effects (McGovern et al. 2015)
  - Heckman-type selection models (Barnighausen et al. 2011, Hogan et al. 2012, Clark and Houle 2014)
  - Adjusting for survey non-response using mortality rates (Nyirenda et al. 2010)

Context: MDR-TB

Multi-drug resistant TB

- Resistant to the two first-line TB drugs
- Indistinguishable from drug-susceptible
- Only 12% of new TB cases tested for MDR globally
- MDR patients comprise:
  - Less than 5% of TB cases
  - 13% of TB deaths
  - 20% of TB spending

Guidelines for MDR testing

- Clinicians observe risk factors
  - TB history
  - Weakened immune system
  - High risk of exposure: prisoners, miners, health workers
- Risk factors are imperfect predictors of MDR
- Cannot test everyone for all possible forms of drug resistance
- Test the proportion of patients θ with highest likelihood of MDR based on observed signal x

Theoretical Model

General model

- Suppose we have a population for which we want to know the mean of outcome y
- We have a routine sample with observations selected to maximize value of y
- Characteristic *x* is observed
- Mapping of *x* to unobservable *y* is not fully known
- Determining value of *y* has associated cost

Key features of clinical decision making

- Patients must be tested before MDR treatment
- Too few resources to test every patient
- Clinician observes noisy signal about patient's likelihood of MDR-TB
- Testing resources determined exogenously:
  - Test materials, lab capacity
  - Funding
  - Clinician awareness and training

Key features of clinical decision making

- Clinician will test patients deemed most likely to have drug-resistance until resources are exhausted
- We assume clinician beliefs about mapping between risk factors and MDR+ is *consistent* within time periods
- Clinicians do not know actual MDR-TB prevalence

Methods

Identification strategy

- Use plausibly exogenous variation in threshold θ to draw inferences about
  - Distribution of y in the population
  - Sampling mechanism
    - Clinician's ability to predict MDR+ based on observable signal x
- Assume consistent beliefs about mapping of x to y
- Regression discontinuity intuition
  - Relax constraint on testing resources

Identification strategy

- Sample means at observed threshold proportion tested θ_0 informative about unobservable x_0:

$$E(y|\theta \leq \theta_0) = E(y|x \geq x_0)$$

- With a binary y, conditional expectation simplifies to:

$$P(y = 1|\theta \leq \theta_t) = \frac{P(\theta \leq \theta_t|y = 1)\mu}{\theta_t}$$

where μ is population prevalence

- Rewriting relationship between y and x in error form:

$$x = \beta_0 + \beta_1 y + e$$

- Normalize β_0 to zero

Estimation

- Rewrite conditional expectation:

$$P(y = 1|\theta \leq \theta_t) = \frac{P(e \geq F_X^{-1}(1 - \theta_t)\text{-}\beta_0\text{-}\beta_1)\mu}{\theta_t}$$

- Assume error term e follows standard normal distribution
- No closed-form (analytical) solution so we use numerical approximation techniques
- Estimate parameter values using maximum likelihood and generalized method of moments
- Grid searches to find most promising parameter space

Policy changes as instrumental variables

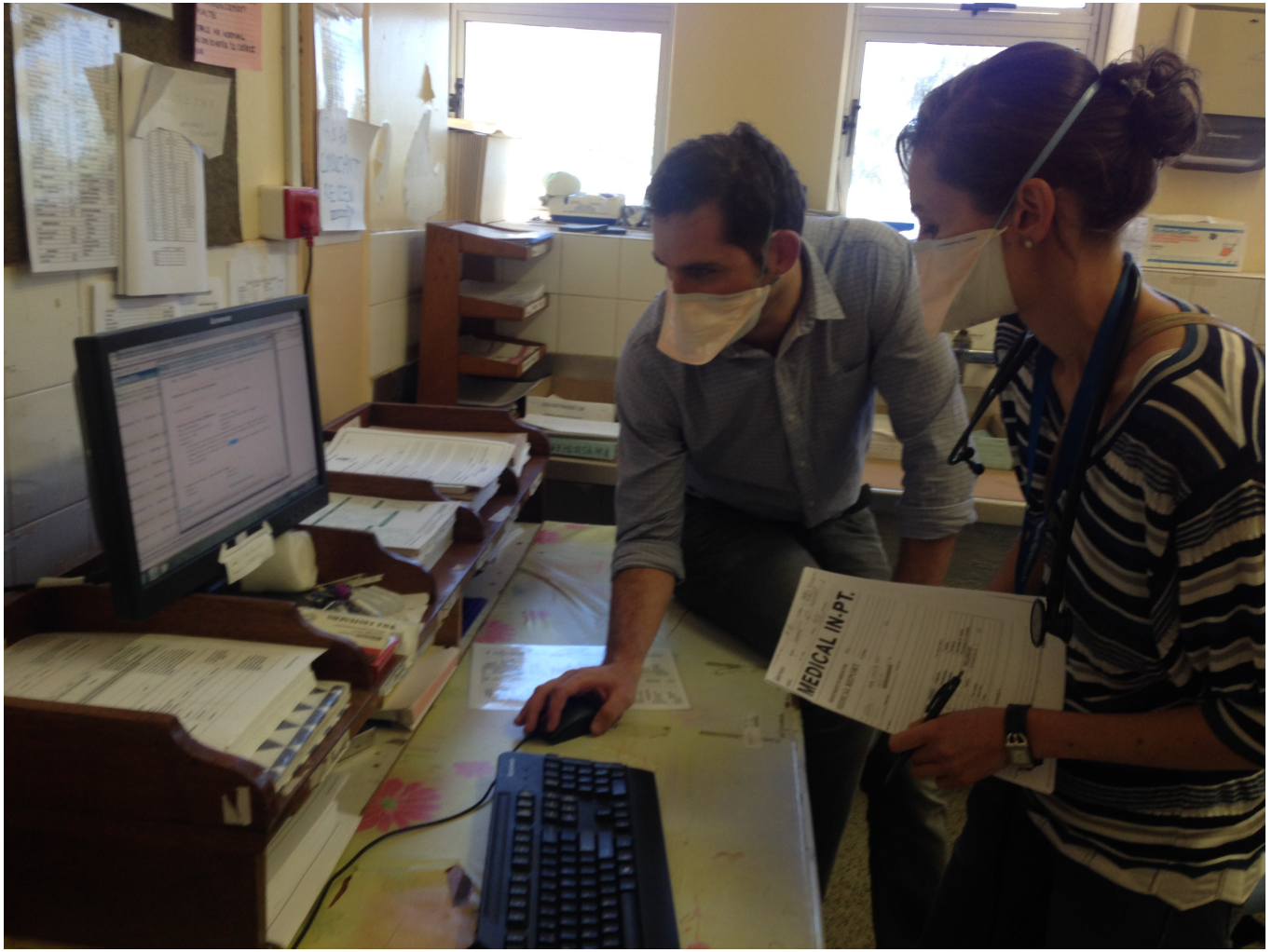
- Exogenous discontinuous changes in testing resources (θ)
  - Time period
  - XDR paper presented at international conference
  - National strategic plan introduced
- Should not affect clinician's understanding of risk factors or the underlying rate of MDR-TB

Data

Data

- National Health Laboratory Service database
- Laboratory database of test results for ~90% of all *suspected* TB cases
  - Jan 2004 – Sept 2010 (Prior to Xpert)
  - 2,190,780 TB+ test results
  - 8,647,12 patients
  - 4,764 health facilities

Accessing NHLS TB database

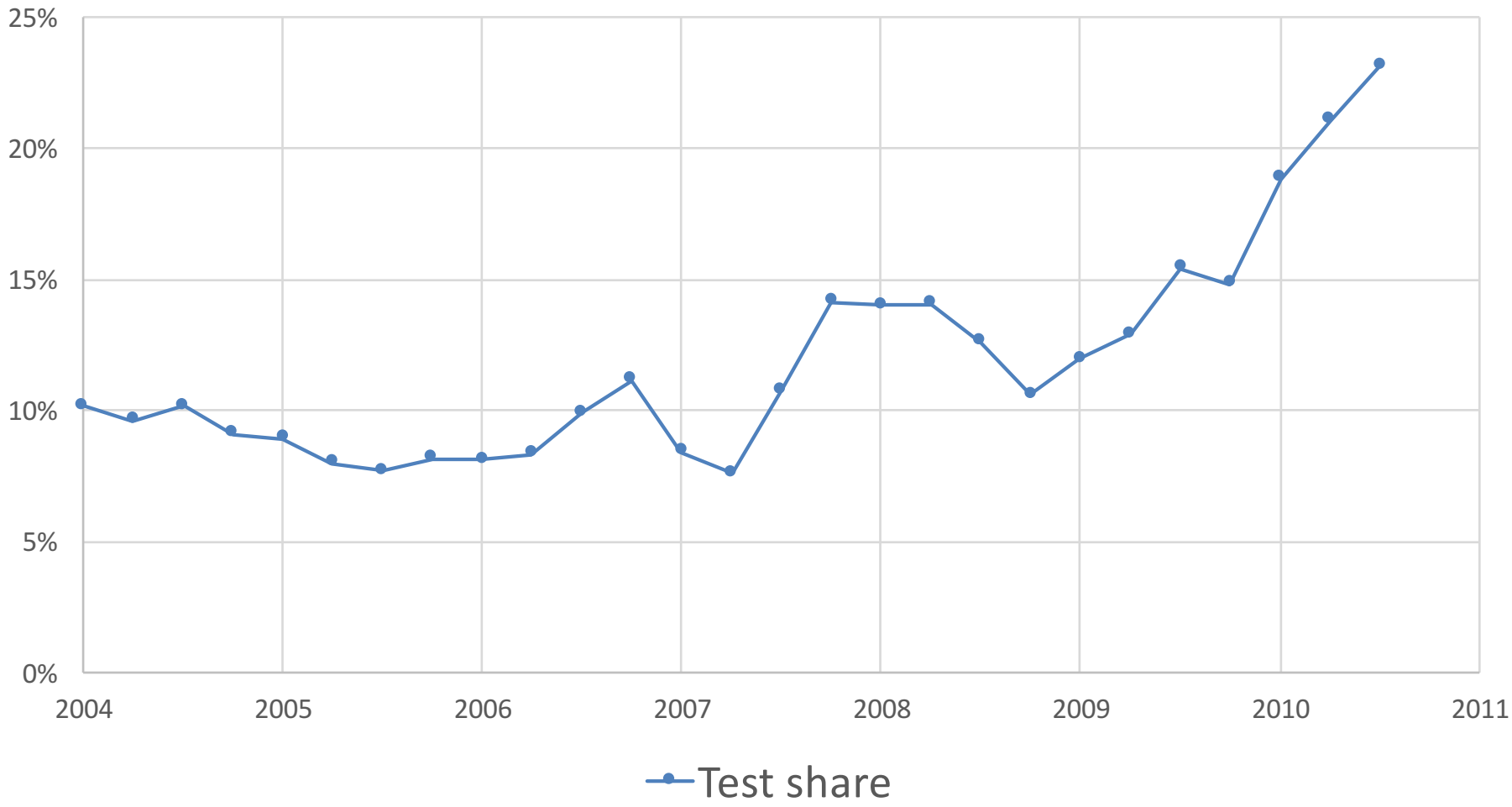


Data

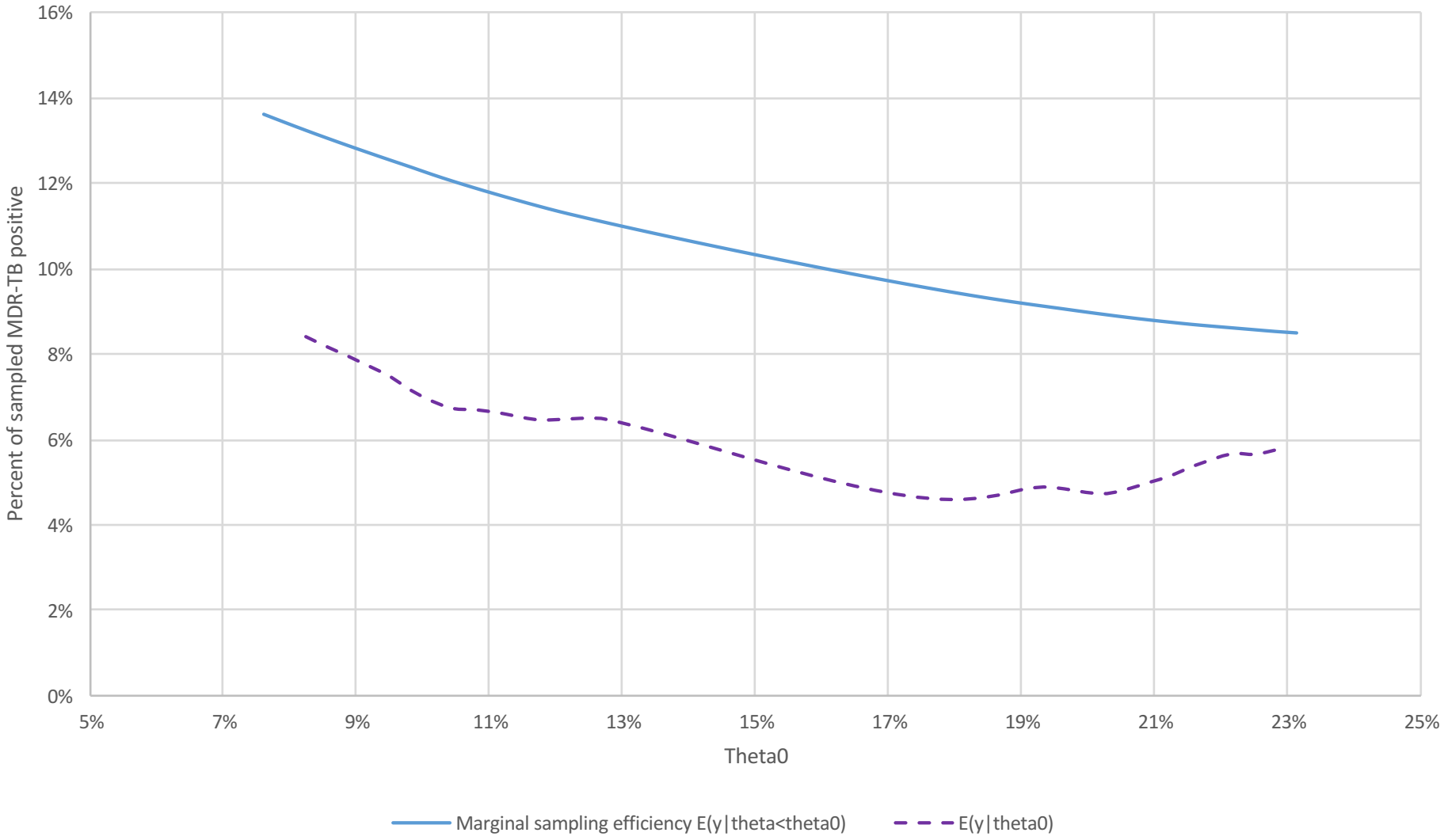
- Examine MDR-TB testing for those who are tested for TB, and have a TB+ result
- Minimal data requirements
- Extract number of patients:
  - TB+ result
  - Tested for MDR
  - MDR+ result

Results

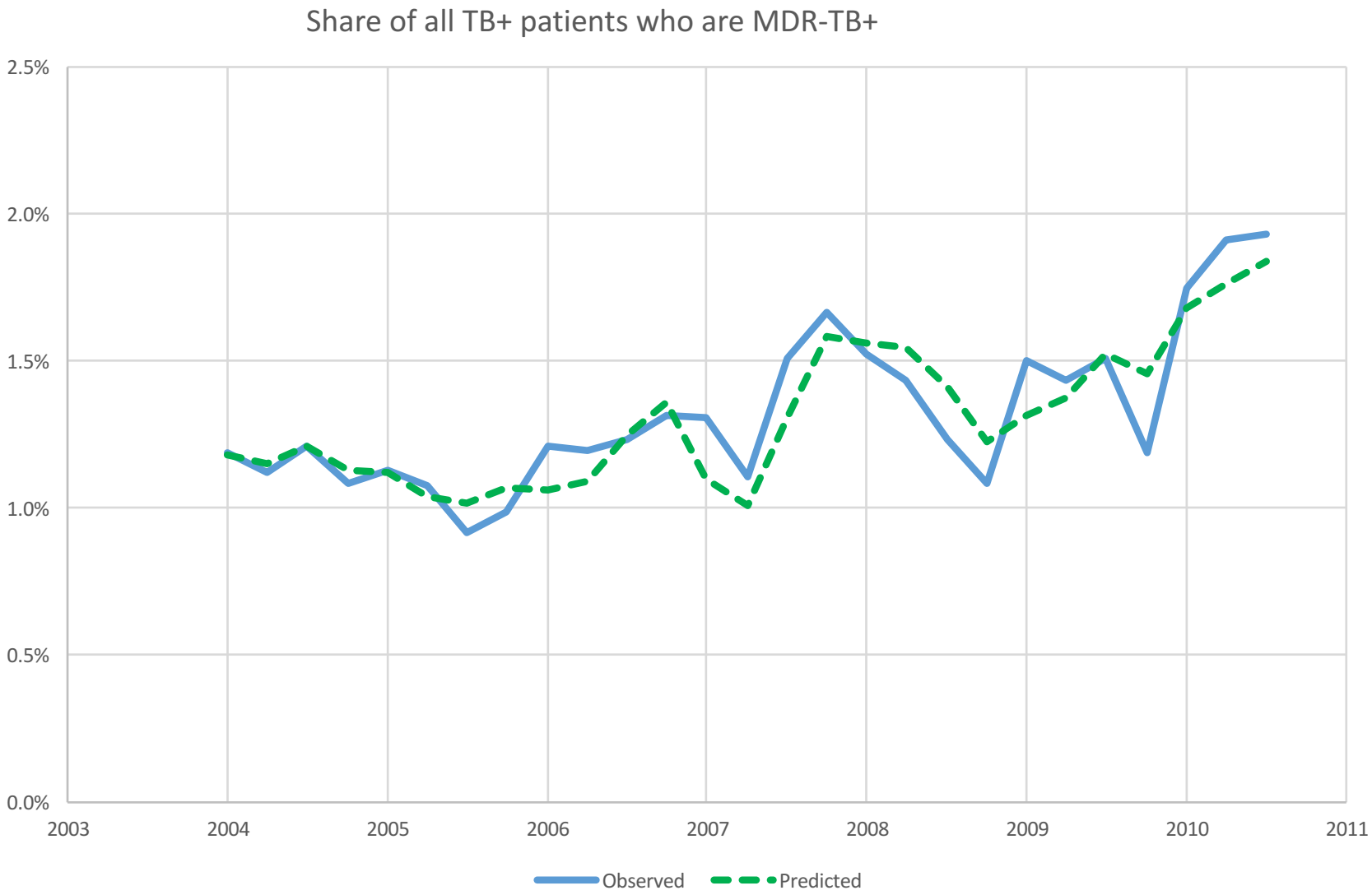
Fraction of TB+ tested for MDR



Sampling efficiency: percent of MDR tested who are MDR+



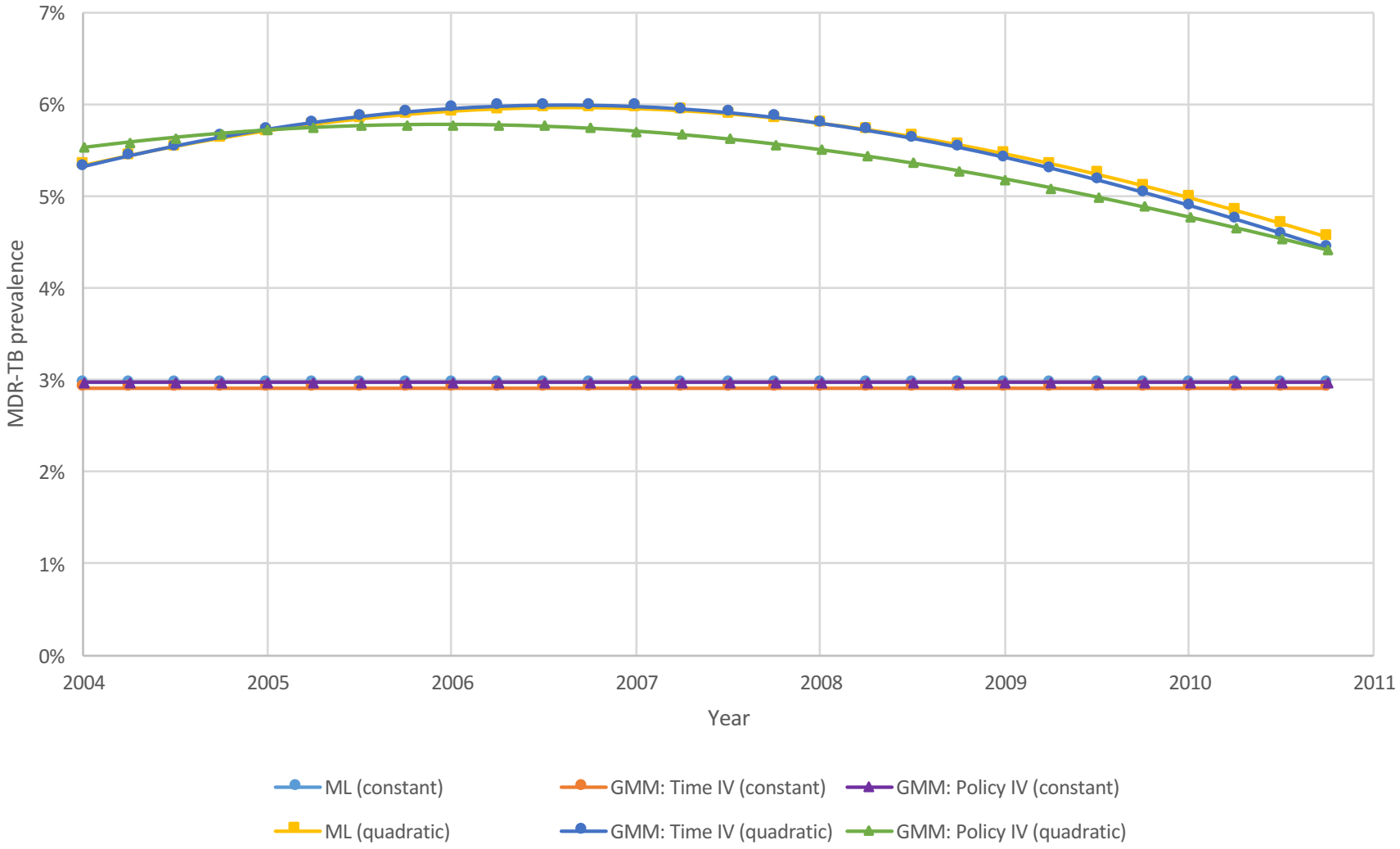
Predicted MDR+ matches observed MDR+ over time



Main results: robustness checks

Method:	ML	GMM	GMM	GMM	GMM
Instruments:		Time	Time	Policies	Policies
	(1)	(2)	(3)	(4)	(5)
Prevalence	0.0305***	0.0298***	0.0342***	0.0305***	0.0301***
	(0.0002)	(0.0013)	(0.0004)	(0.0016)	(0.0004)
Signal-to-noise	1.0749***	1.0891***	0.9336***	1.0716***	1.0846***
	(0.0003)	(0.0489)	(0.0117)	(0.057)	(0.0142)
Observations	262,845	262,845	262,853	262,850	262,842
Clustering	No	No	Yes	No	Yes
Pseudo R^2 #1	0.694	0.699	0.529	0.691	0.703
Pseudo R^2 #2	0.695	0.695	0.694	0.695	0.696
Log likelihood	-90646.845				
GMM criterion		0.00131	0.01626	0.00044	0.0078

Quadratic MDR-TB time trend estimates



Conclusions

- Evidence that “official” MDR rates are too low
  - 16-26% of MDR cases were undiagnosed
  - More resources are needed
- Routine data can provide real-time tracking
  - Widely available and under-used
  - Valuable where cannot test everyone or where compliance with guidelines < 100%
- Clear applications beyond TB

Thank you!