Example of Bias Analysis: Influenza Vaccination Misclassification and Preterm Birth

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Background: Flu shot

- CDC recommends all pregnant women be vaccinated for influenza
  - Vaccination rates increasing, but still low
  - Barriers to vaccination include concerns about risks to fetus
- Not many studies on influenza vaccination and pregnancy outcomes
  - Pregnant women excluded from most clinical trials
  - Recently published observational study found strong protective effect (40% reduction in risk)

Study Hypothesis

Influenza vaccination will be associated with a decreased risk of preterm birth

Prenatal Vaccination Exposure: Potential for Misclassification

- Medical records:
  - May not be accurate; many flu vaccinations outside of traditional medical settings
- Self-report:
  - Possibly better because captures full range of vaccine providers; but could be subject to NDME and/or DME (recall bias)

Slone Pregnancy Health Interview Study

- Case-control study
- Multicenter (Mass., RI, upstate NY, Philadelphia, San Diego)
- Hospital and vital records-based
- 1976 – present
- Mothers interviewed <6 months of birth
  - Medical history, pregnancy intention, medication use, demographics, smoking and alcohol consumption

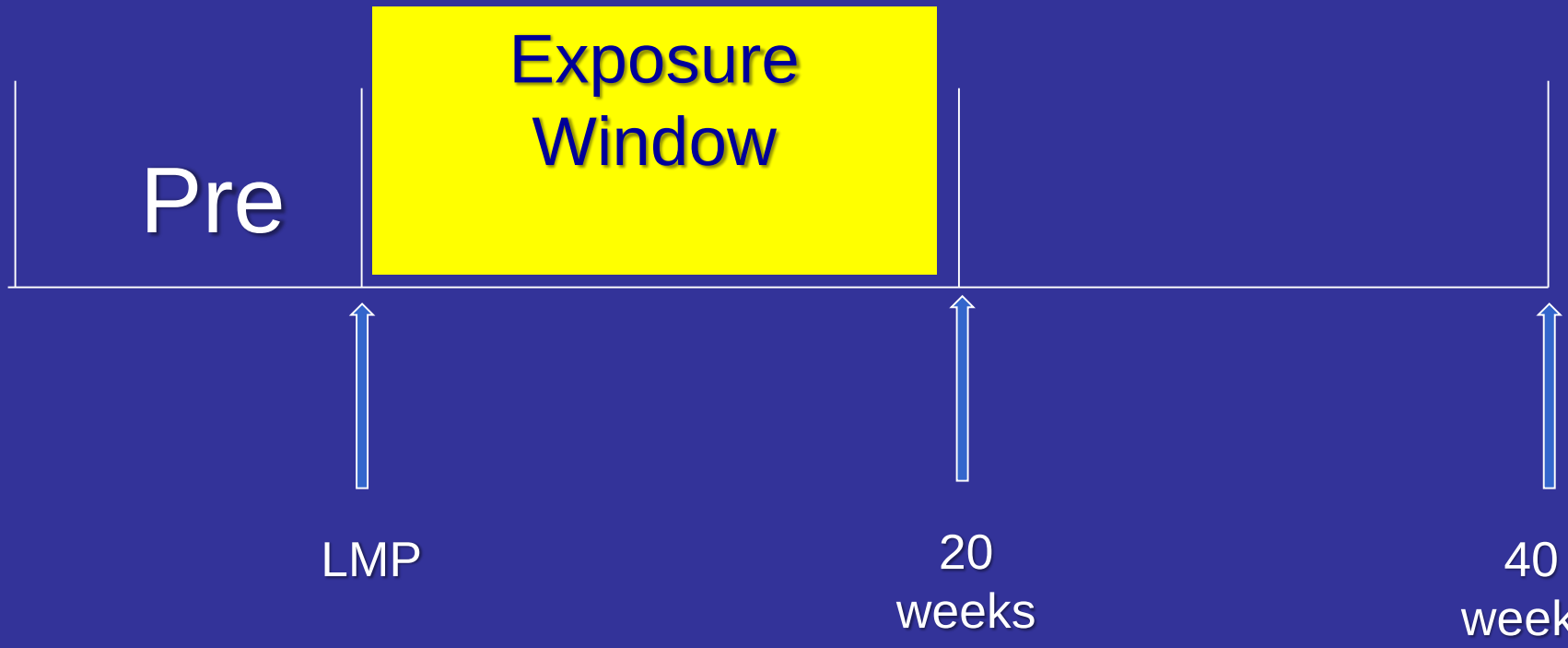
Methods: Exposure Assessment

- Beginning in September 2006 all mothers were asked if they received any vaccines:

  "such as tetanus, pertussis, whooping cough, meningitis, flu shot or any other vaccine" during the period two months before through the end of the pregnancy
- If a single date not recalled, then asked to recall range of possible dates

Methods: Exposure Window

- Exposure: any flu shot reported during 0-20 week's gestational age



Methods: Outcome

- Preterm < 37 weeks; full-term ≥ 37 weeks
- Self-reported due date (usually ultrasound confirmed)
- Calculate gestational day of delivery using 280- (due date - baby's date of birth)

Methods: Validation Sub-study

- All women who reported influenza vaccination
  - Asked to sign vaccine medical release form
  - Date, vaccine type, manufacturer obtained from provider
  - Staff tracked validation efforts
- Very labor intensive

Methods: Regression

- Logistic regression
- Exposure: influenza vaccination 0-20 weeks
- Outcome: preterm (case) vs. full-term (control)
- Restricted to:
  - Infants without birth defects
  - Mothers reporting influenza vaccination 0-20 weeks or no prenatal influenza vaccination
  - N=1752

Methods: Bias Analysis

- Couldn't estimate sensitivity/specificity
- Could estimate: positive predictive value (PPV) of self-reported flu shot at any time before/during pregnancy
- PPV calculated using:
  - $\frac{\text{\# confirmed flu shot}}{\text{\# self-reported flu shot}}$
  - Separately estimated for preterm (cases) and full-term (controls) pregnancies

Methods: Tracking Status

- Could only confirm flu shot if:
  - Med release returned, provider could be reached + cooperated, and patient-level information was available
- 2 ways of calculating PPV:
  - Less conservative: Upper PPV estimate
    - If flu vaccination date was found, staff determined if inside/outside pregnancy dates
  - More conservative: Lower PPV estimate
    - Also included situations where no vaccination date was found or vaccination recalled was not actually flu shot

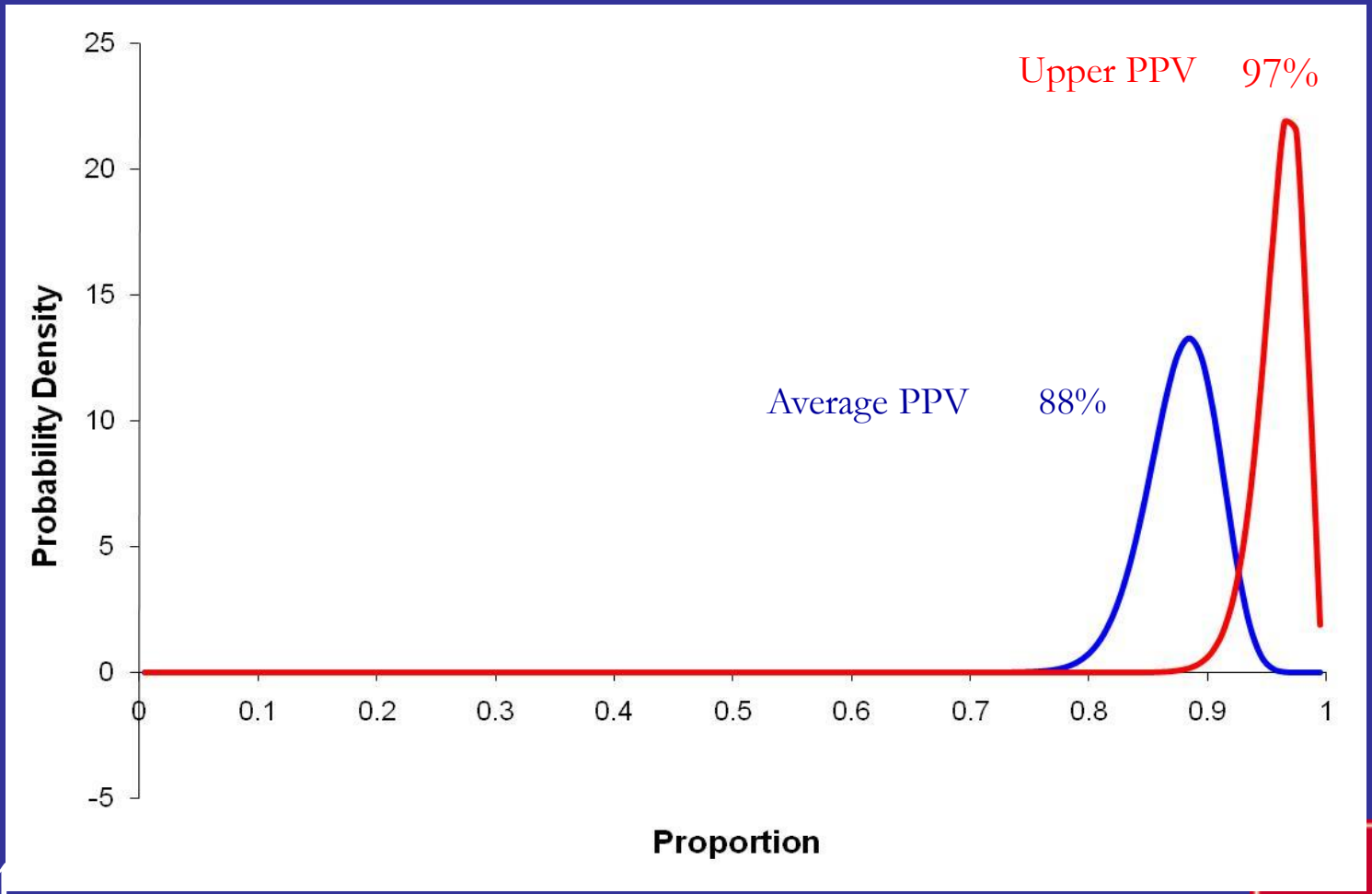
Methods: PPV Estimates

	Upper PPV	Lower PPV
Preterm	97%	79%
Full-term	95%	78%

- Similar PPV between preterm and full-term: supports NDME
- In addition to upper PPV, calculated a weighted average of upper/lower PPV

Methods: PPV Beta Distributions

- Preterm:



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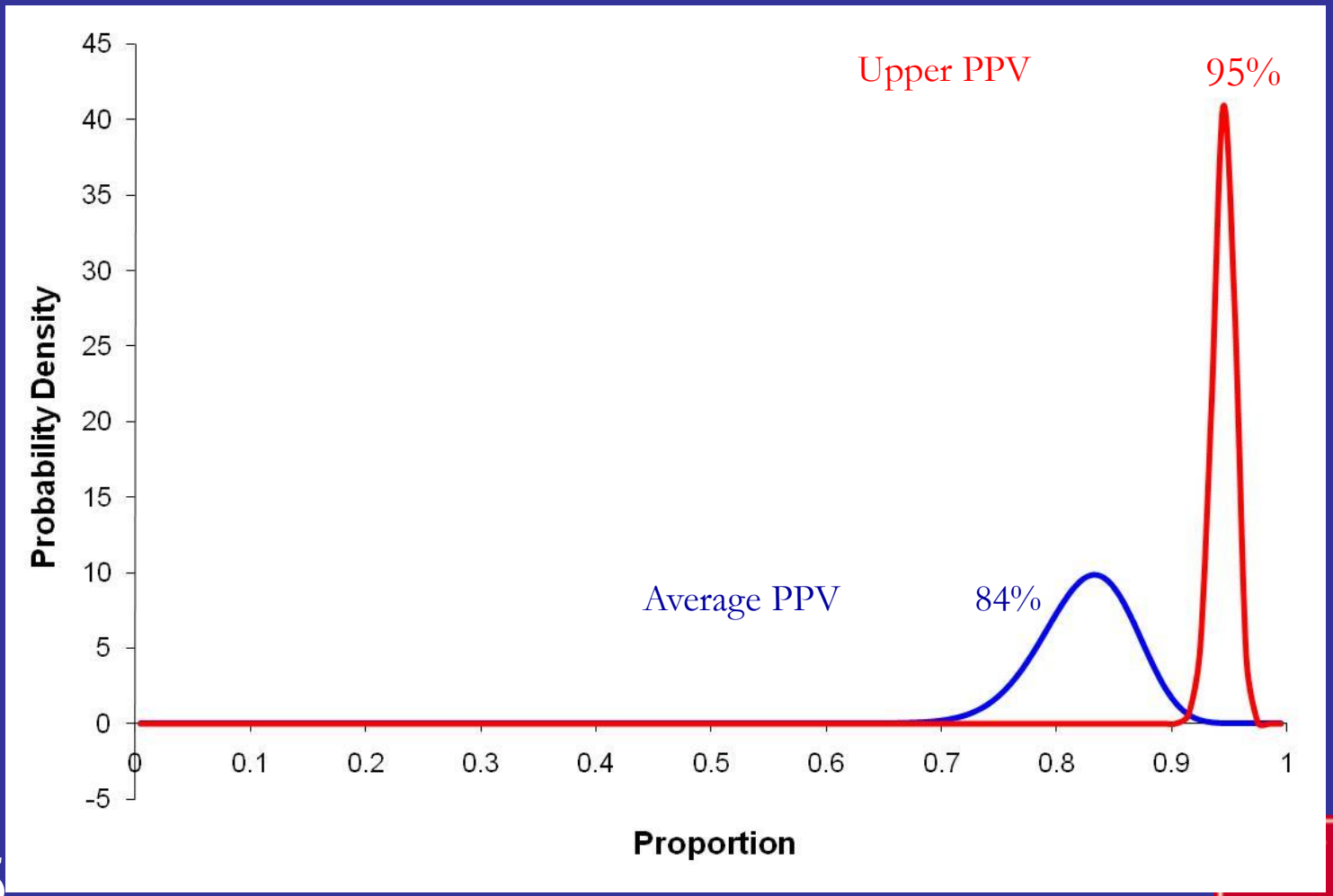
Methods: PPV Beta Distributions

- Full-term:



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Methods: Bias Analysis

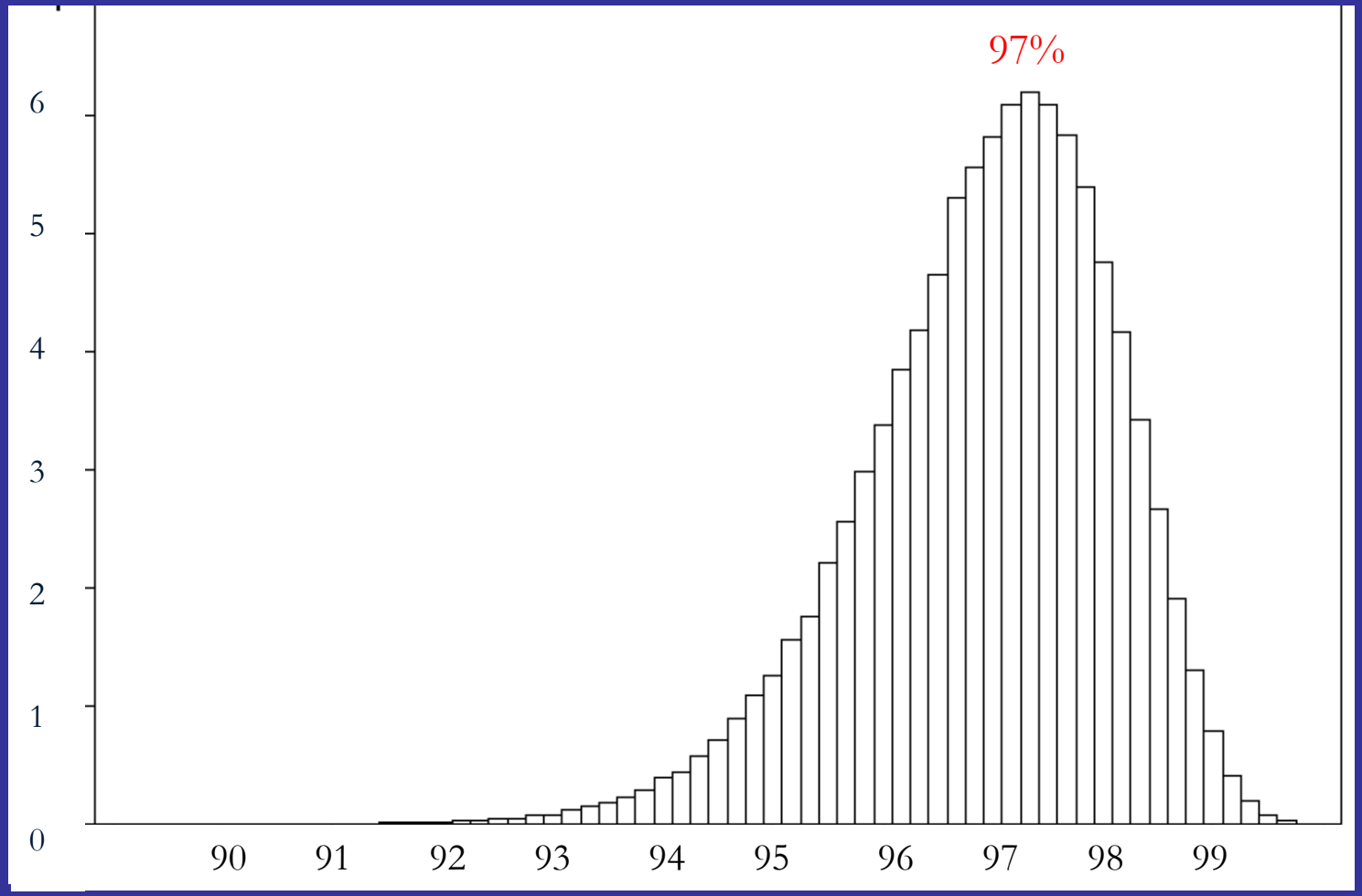
- Negative Predictive Value
- NPV can be calculated using:
  - $\frac{\text{\# confirmed no flu shot}}{\text{\# reported no flu shot}}$
  - Separately for preterm and full-term
  - We didn't have this information from our validation sub-study

Methods: Bias Analysis

- Alternative calculation of NPV
  - NPV= $\frac{(spec)(1-Pe)}{(spec)(1-Pe) + (1-sens)(Pe)}$
  - uses prevalence of self-reported exposure (Pe)
  - sensitivity/specificity from 2007 Mangtani validation study, asked about flu shot in last 12 months
    - Among 354 elderly persons in UK
    - Sens= 190/201=93% ; Spec= 138/153=85%

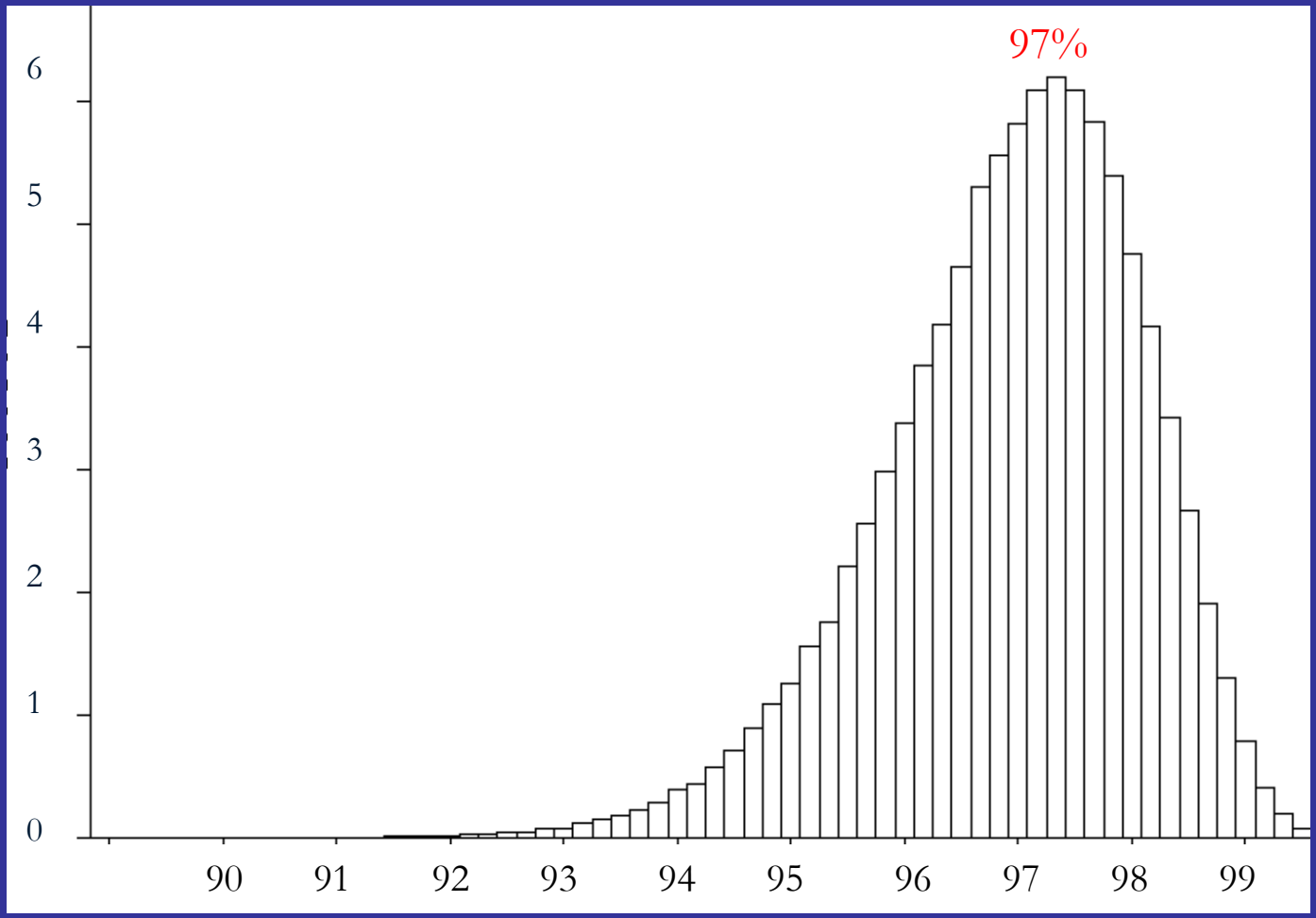
Methods: NPV Model

- Preterm:



Methods: NPV Model

- Full-term:



Methods: Observed data

	Vaccinated	Not vaccinated
Preterm	35 (9%)	104 (7.6%)
Full-term	353	1260
All	388	1364

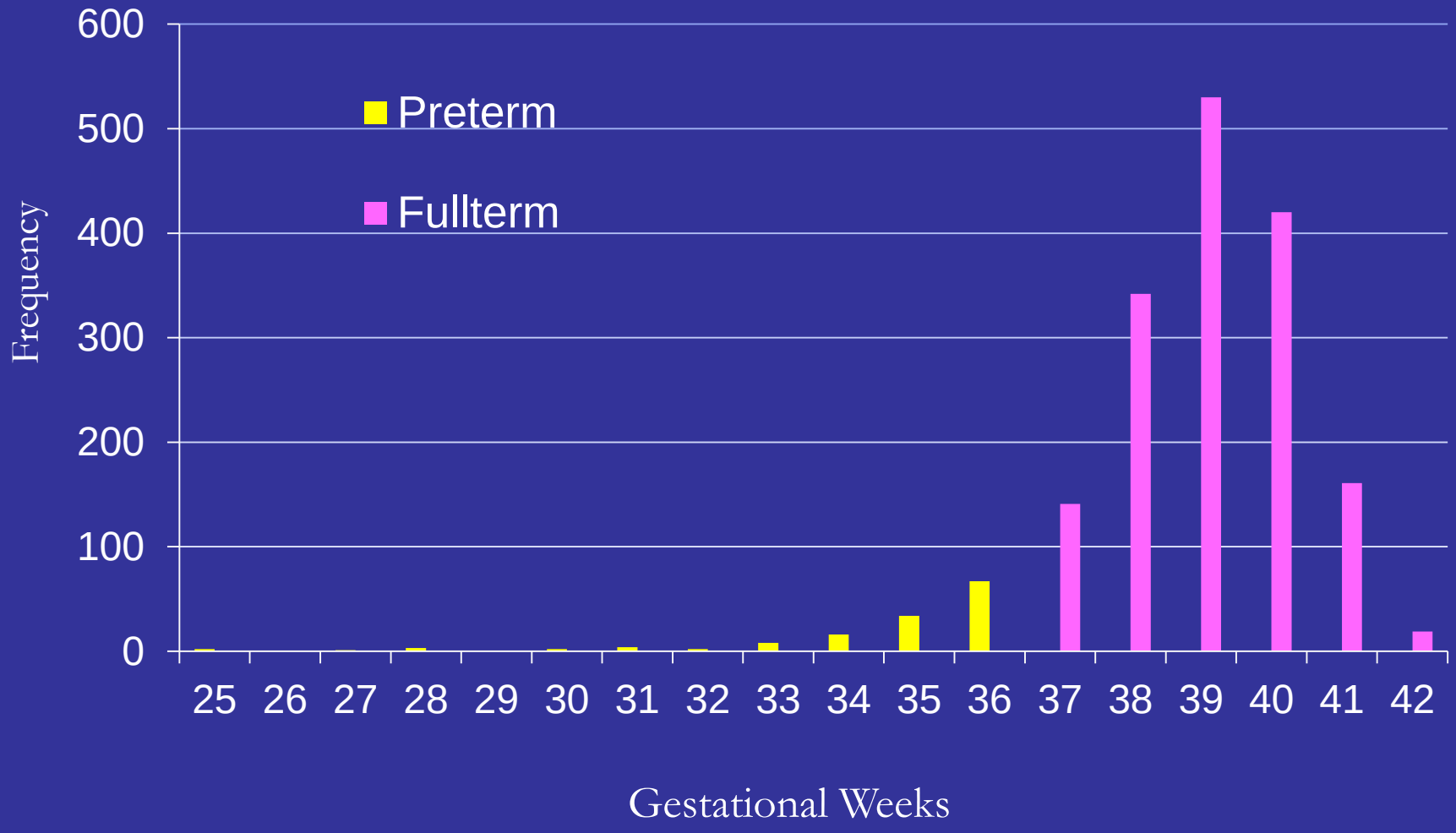
- OR, Crude: 1.20 (0.80, 1.79)
- OR, Adjusted: 1.21 (0.79, 1.88)
  - For maternal race, multifetal gestation

Methods: Simulation Example

Rep=1
Rep=2
Rep=3
. . . . .
Rep=100,000

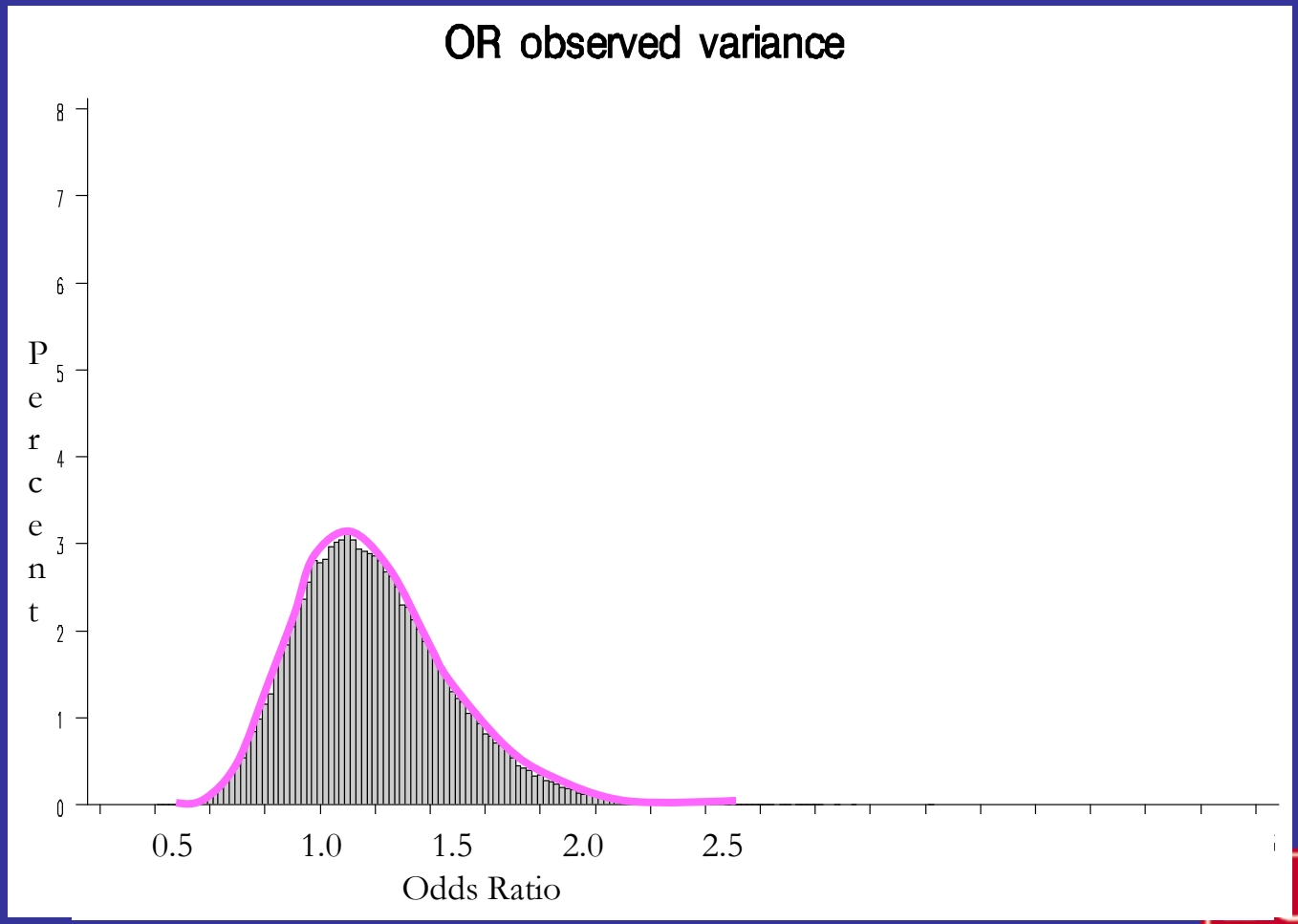
- 100,000 datasets stacked
- Look at Replication=1:
  - PPVpreterm=0.88
  - PPVfull-term=0.75
  - NPVpreterm=0.97
  - NPVfull-term=0.97
- 388/1752 records where observed exposure status =1; after bias correction, now 334
- 1364/1752 records where observed exposure =0; after bias correction now 1416
- Simulation Rep 1 Adj OR=1.61

Results: Gestational Age



Simulated Distribution of Obs OR

OBS OR 1.21 (0.79, 1.88)



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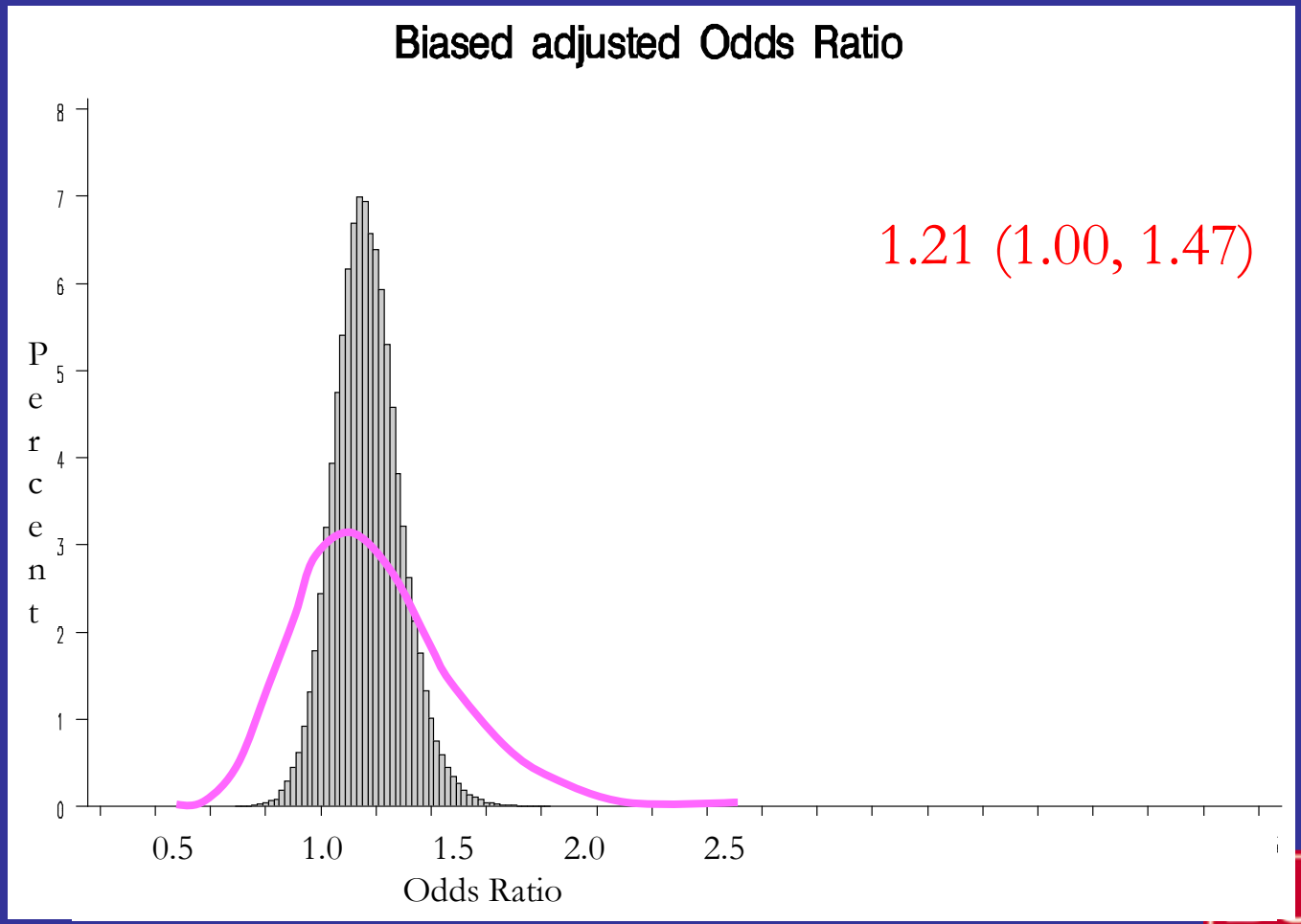
Bias Adjusted OR

OBS OR 1.21 (0.79, 1.88)

- Upper PPV



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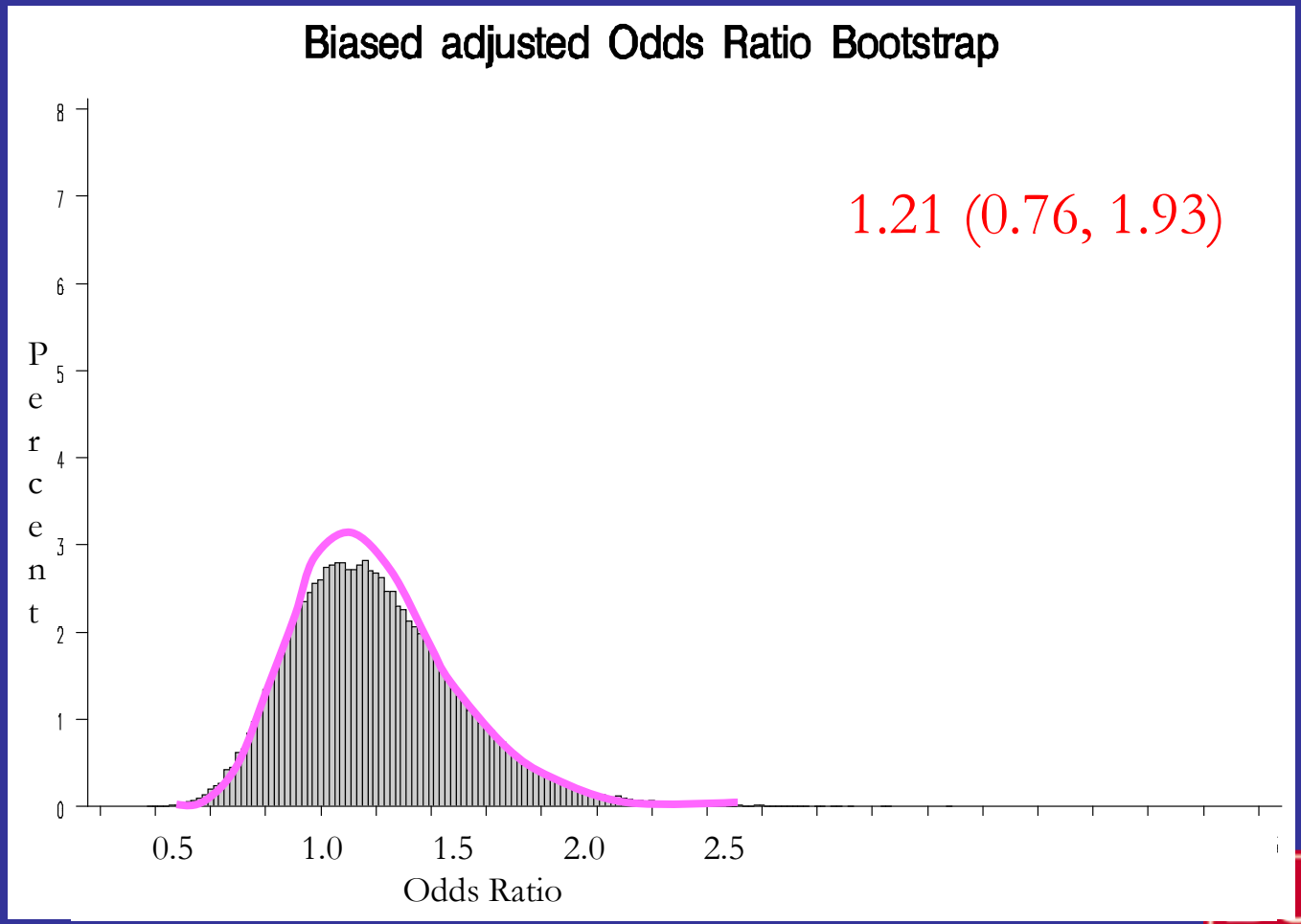
Bias Adjusted OR + Random Error

- Upper PPV

OBS OR 1.21 (0.79, 1.88)



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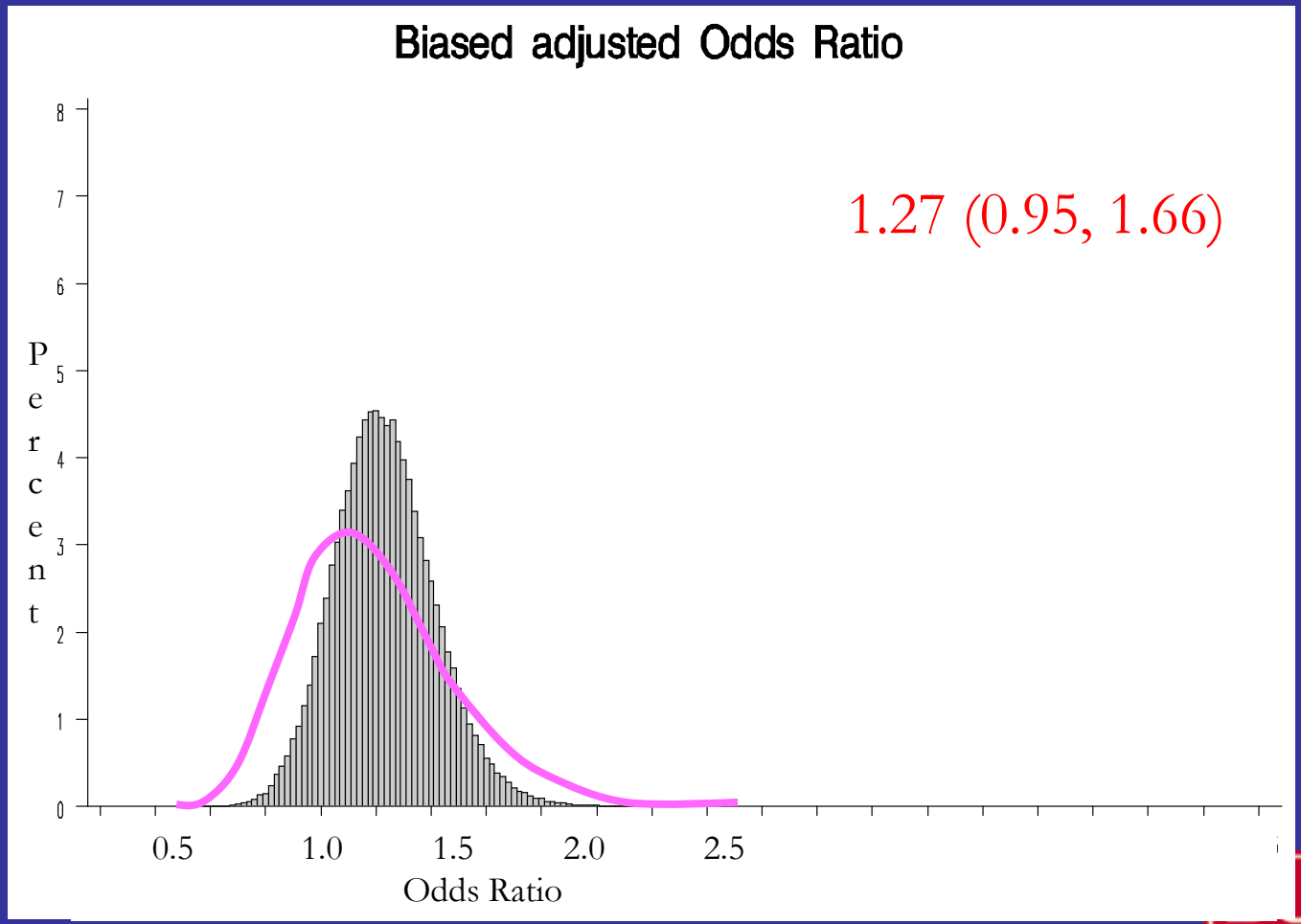
Bias Adjusted OR

- Average PPV

OBS OR 1.21 (0.79, 1.88)



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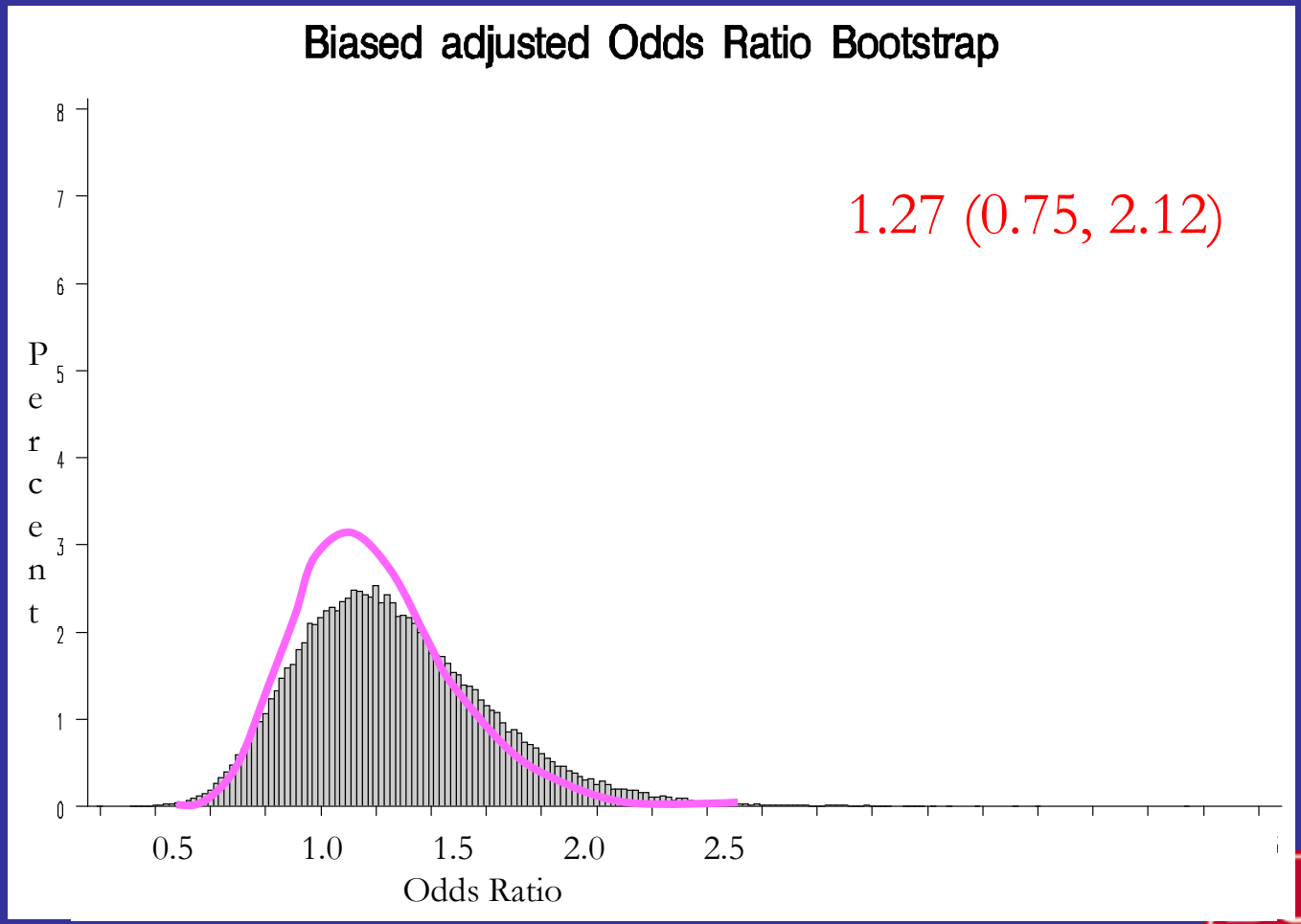
Bias Adjusted OR + Random Error

- Average PPV

OBS OR 1.21 (0.79, 1.88)



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Conclusion:

- Appears to be a near null effect of influenza vaccination during 0-20 week's gestation on risk of preterm birth
- Adjustment for misclassification of exposure changed estimates minimally
- General study limitations:
  - No information on effect of flu shot on miscarriage, stillbirth, early preterm risk

Possible Bias Model Limitations

- Other predictors of PPV? Education, GA, age…
- Applicability of overall prenatal PPV estimate to our 0-20 week window?
- Applicability of NPV from external validation study?
  - Back-calculated PPV: 83%
- NPV calculation used observed prevalence of exposure, some error

Advantages: Bias Modeling

- Using record level modeling, so could still adjust for confounders
- SAS code was straightforward
- Now more confident that misclassification of vaccination status is not what is accounting for observed near null results
- Useful to see no (major) differential exposure misclassification based on preterm/full-term status

Disadvantages: Bias Modeling

- To do bias modeling with internal validation data can be expensive and labor intensive
  - Other exposures/methods could be cheaper to validate; very cheap to use external validation data
- Explaining methods, results, and limitations of bias modeling takes up space
  - Worth it to assess possible bias that could be much larger issue than random error

Collaborators

- Martha Werler
- Timothy Lash
- Carol Louik
- Allen Mitchell

- Preliminary analysis; *incomplete data*
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THANK YOU