# Bayesian Statistics & Real World Evidence: A Successful Example from CBER

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# DISCLAIMER

This presentation is an informal communication and represents my own best judgement. My comments do not bind or obligate FDA.

# PERTUSSIS (WHOOPING COUGH)

- Highly contagious severe respiratory disease

- Infants at high risk of severe disease because airways are small
  - High risk of hospitalization and death
  - ~100 cases per year in infants (< 1 year old)

- Vaccines are highly effective at preventing disease
  - Herd immunity, though some declines recently (hesitancy)
  - Childhood vaccination starts at 6 months of age

# MATERNAL IMMUNIZATION

- Immunization of pregnant person during pregnancy to protect newborn via
  - Passively transferred antibodies (placenta and breastmilk)
  - Cocooning (family members less likely to infect infant)

- CDC ACIP recommended off-label use for pertussis vaccines since 2012
  - Based on observational studies and scientific understanding
  - Recommends vaccination at 27-36 weeks (~ 3rd Trimester)
  - Despite recommendation, adoption is low in US (~40%)

# MI FOR PERTUSSIS

- Public health priority to have labeling claim
  - Increase confidence in use, insurance coverage
  - Reflect scientific understanding and quantify benefit
- However, an RCT would be infeasible:
  - Placebo-controlled RCT unethical because of ACIP recommendation (no equipoise?)
  - Non-inferiority trial infeasible because no licensed comparator
  - Small number of cases per year adds difficulty

# MI FOR PERTUSSIS

- Alternative: use RWD, *if* fit-for-purpose RWD exists
- Pertussis is a notifiable disease
  - CDC has lab-confirmed cases in US
- Off-label TDaP use for this indication
  - TDaP vaccines are licensed for use in US adults
  - CDC recommendation for off-label use

# MI FOR PERTUSSIS: DATA (Skoff 2017)

- Retrospective case-control study of CDC surveillance data
- Age-matched controls (3:1) from same birth hospital
- Collected information on 3 most recent Td/TdaP exposures
  - Timing
  - Manufacturer/brand/lot
- Estimated vaccine effectiveness
  - overall
  - 3rd trimester
- No brand specific results

*Skoff, et al. 2017. Impact of the US Maternal Tetanus, Diphtheria, and Acellular Pertussis Vaccination Program on Preventing Pertussis in Infants < 2 Months of Age: a Case-Control Evaluation, Clin Infect Dis, 65(12)*

# MI FOR PERTUSSIS: EXPOSURE DATA

- Exposure classified based on most recent Td/Tdap vaccination
  - Unexposed
  - Before pregnancy
  - 1st/2nd Trimester (~0-27 weeks)
  - 3rd Trimester (~28-40+ weeks)
  - After birth
- However, exposure could be ambiguous
  - Vaccine type (Td/TdaP) unknown
  - Many mothers were exposed multiple times, including during or after pregnancy
  - Ambiguous or unknown manufacturer/brand

# MI FOR PERTUSSIS: DATA (Skoff 2017)

| Pertussis Exposure Timing | Cases (%) | Controls (%) |
|---|---|---|
| Unexposed | 111 (44) | 276 (41) |
| Before Pregnancy | 25 (10) | 88 (13) |
| 1st/2nd Trimester | 7 (3) | 33 (5) |
| *3rd Trimester* | *18 (7)* | *109 (16)* |
| After Birth | 90 (36) | 176 (26) |

3rd Trimester Adjusted VEff:
77.7% (95% CI: -13.8%, 88.8%)

# MI FOR PERTUSSIS: BY BRAND

- CDC's brand-agnostic results are promising (point estimate), but uncertain (wide CI)
- Brand-specific 3rd Trimester results required for labeling
- However, small number of 3rd trimester exposed participants in brand specific datasets

| Vaccine | Summary (Exposed/Total) |
|---|---|
| Adacel | Cases: 5/101<br>Controls: 27/171 |
| Boostrix | Cases: 4/108<br>Controls: 18/183 |

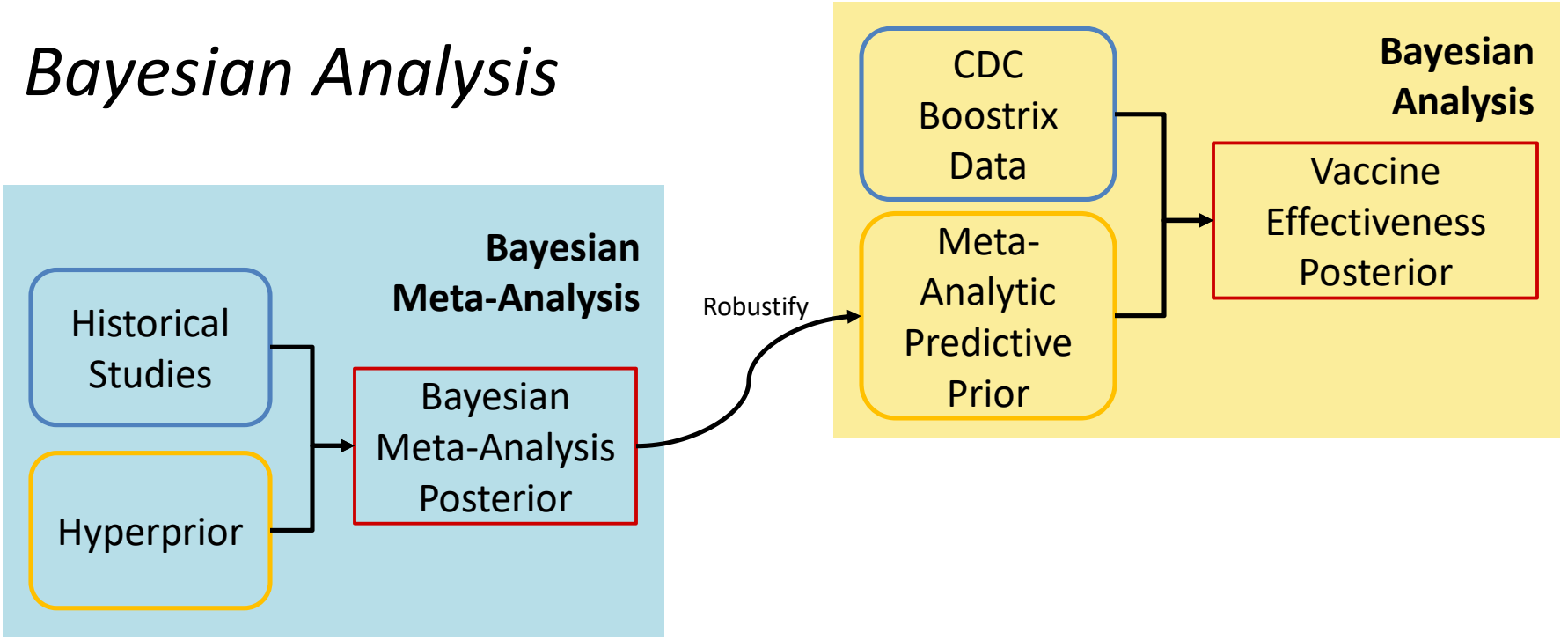
Note: Numbers here do not sum to totals shown on previous slide because of missing/ambiguous data

# MI FOR PERTUSSIS: APPROACHES

- Adacel (Sanofi)
  - Conditional logistic regression of the data from infants whose mothers were unexposed or exposed to Adacel during the 3rd trimester
  - Vaccine Effectiveness (95% CI): 88.0 (43.8, 97.4)
- Boostrix (GSK)
  - Bayesian analysis of the data from infants whose mothers were unexposed or exposed to Boostrix during the 3rd trimester using a prior based on a Bayesian meta-analysis

# MI FOR PERTUSSIS: BOOSTRIX

*Bayesian Analysis*



# MI FOR PERTUSSIS: BOOSTRIX

*Bayesian Meta-Analysis: Historical Studies*

- Published studies of Boostrix IPV (non-US formulation)
- Applicant submitted data to support comparability of the immune response to US and non-US Boostrix formulations
- Literature review yielded 4 studies with similar study designs and Boostrix-specific vaccine effectiveness estimates
  - 2 case-control studies
  - 2 case-coverage studies

# CASE-CONTROL STUDIES

| Study Design | Bellido-Blasco (Spain) | Saul (Australia) |
|---|---|---|
| Mat. Vax. Advice | Recommended, Jan 2015 | Campaign, Apr 2015 |
| Study Dates | Mar 2015-Feb 2016 | Aug 2015 – Aug 2016 |
| Mat. Vax. Timing | 3rd T, > 2wk before birth | 1-3rd T, > 2wk before birth |
| Case Definition | + RT-PCR | Symptoms + lab confirm |
| Cases: Age, Tdap Exp. | < 3 mo, unvax | < 3 mo, not specified |
| Control:Case Matching | 3:1 on age (± 15 days) | 1:1 on birthdate (± 3 days) |
| Control Ascertainment | 2 med pract, 1 matern clinic | 1 public hosp. same district |

# CASE-COVERAGE STUDIES

| Study Design | Andrews (England) | Uriarte (Spain) |
|---|---|---|
| Mat. Vax. Advice | Campaign, Oct 2012 | Recommendation, Feb 2015 |
| Study Dates | Sept 2014-Sept 2018 | Feb 2015 – Jan 2016 |
| Mat. Vax. Timing | $2^{nd}$-$3^{rd}$ T, > 7 days before birth | $3^{rd}$ T |
| Case Definition | Lab-confirmed | 95% confirmed by PCR |
| Cases: Age | < 3 mo | < 3 mo |
| Coverage Data Source | CPRD | Immunization Data/Registry |
| Coverage Estimates | ~60-80% stratified by mat age in years (< 28, 28-32, ≥33) | 93.7% |

# MI FOR PERTUSSIS: BOOSTRIX

*Bayesian Meta-Analysis: Historical Studies*

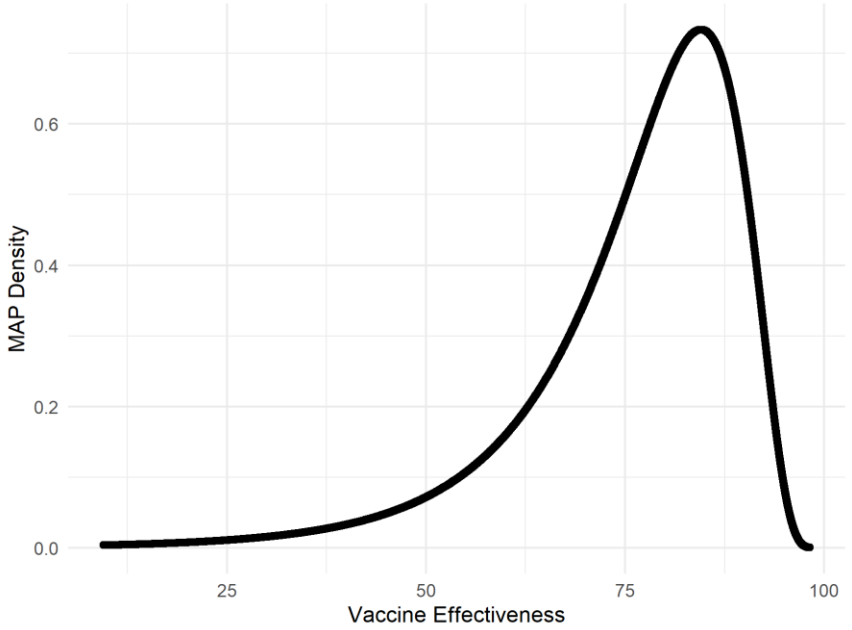
| Study | Summary (Exposed/Total) | VEff (95% CI) |
|---|---|---|
| Bellido-Blasco | Cases: 5/22<br>Controls: 41/66 | 87% (34%, 98%) |
| Saul | Cases: 19/48<br>Controls: 33/48 | 64% (18%, 84%) |
| Andrews | Cases: 106/403 | 87% (84%, 90%) |
| Uriarte | Cases: 12/19 | 89% (72%, 96%) |

# MI FOR PERTUSSIS: BOOSTRIX

*Bayesian Meta-Analysis: Results*

- Hyperpriors (on log-odds):
  - Mean: Normal(0, 1,000,000)
  - SD: Half-Normal(0, 0.5)

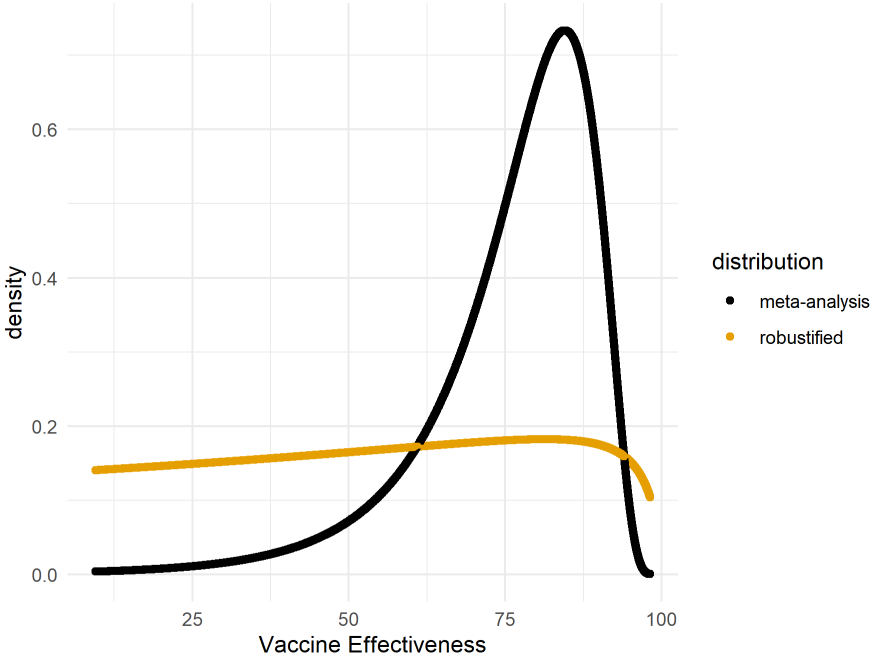
- Produced posterior distribution for VEff



# MI FOR PERTUSSIS: BOOSTRIX

*Bayesian Meta-Analysis: Robustified Results*

- Mixture of the meta-analysis and a vague prior:
  - Normal(0, σ)
  - σ: observed SE for log-odds of an individual subject from CDC Boostrix-specific data
- Mixture weights
  - 90% meta-analysis
  - 10% vague



# MI FOR PERTUSSIS: BOOSTRIX

*Bayesian Analysis: Results*

- VEff (95% Credible Interval) reported in the label:
  - 20% informative prior weight: 81.5 (12.9, 94.5)
  - 90% informative prior weight: 83.4 (55.7, 92.5)
- FDA requested several sensitivity analyses
  - Various prior mixing weights, leave-one-out for prior studies
  - Ambiguous/multiple exposures
  - Inclusion of participants with missing demographic data
  - Inclusion of participants with missing manufacturing/brand data
- Sensitivity results were consistent with those reported in the label

# REAL-WORLD DATA CONSIDERATIONS

- Good candidate for RWD/RWE because of ethical issues and public health need
- Challenges with real-world data
  - Third-party data owner complicated review
  - Fixed, small sample size
  - Ambiguous data: no pre-specified way to address
- Access to data was key for FDA review

# BAYESIAN ANALYSIS CONSIDERATIONS

- Justification of informative prior as relevant and specific to product and indication is critical
  - Immunogenicity data to justify application of non-US Boostrix VEff estimates
  - Boostrix-specific estimates of VEff, not just generic estimates for pertussis vaccines
- Needed more time for review under both IND and BLA
  - Time to come to a scientific consensus
  - Time for internal review of approach and data
- Label was complex
  - Concerns about health care providers' understanding of Bayesian statistics
  - How to accurately convey prior information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