OHDSI + FDA CBER: Improving vaccine safety surveillance

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RESEARCH ARTICLE

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Bayesian safety surveillance with adaptive bias correction

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Postmarket safety surveillance is an integral part of mass vaccination programs. Typically relying on sequential analysis of real-world health data as they accrue, safety surveillance is challenged by sequential multiple testing and by biases induced by residual confounding in observational data. The current standard approach based on the maximized sequential probability ratio test (MaxSPRT) fails to satisfactorily address these practical challenges and it remains a rigid framework that requires prespecification of the surveillance schedule. We develop an alternative Bayesian surveillance procedure that addresses both aforementioned challenges using a more flexible framework. To mitigate bias, we jointly analyze a large set of negative control outcomes that are adverse events with no known association with the vaccines in order to inform an empirical bias distribution, which we then incorporate into estimating the effect of vaccine exposure on the adverse event of interest through a Bayesian hierarchical model. To address multiple testing and improve on flexibility, at each analysis time-point, we update a posterior probability in favor of the alternative hypothesis that

Vaccine → adverse event??

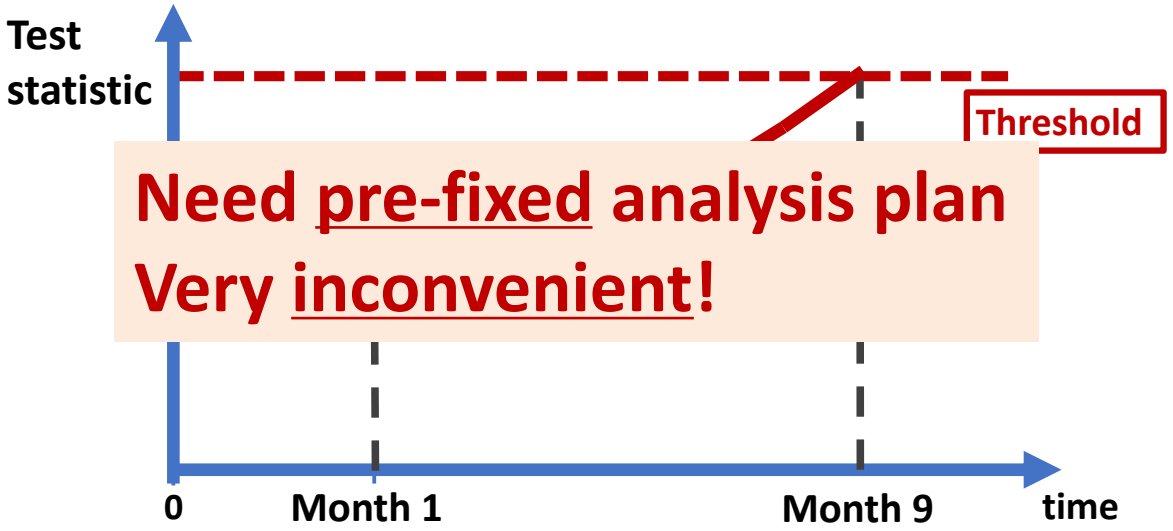
- Post-market surveillance (clinical trials unable to detect rare & severe events)
- Hypothesis testing:

H_0: no increased risk v.s. H_1: increased risk

- Sequential analysis of real-world data as they accrue

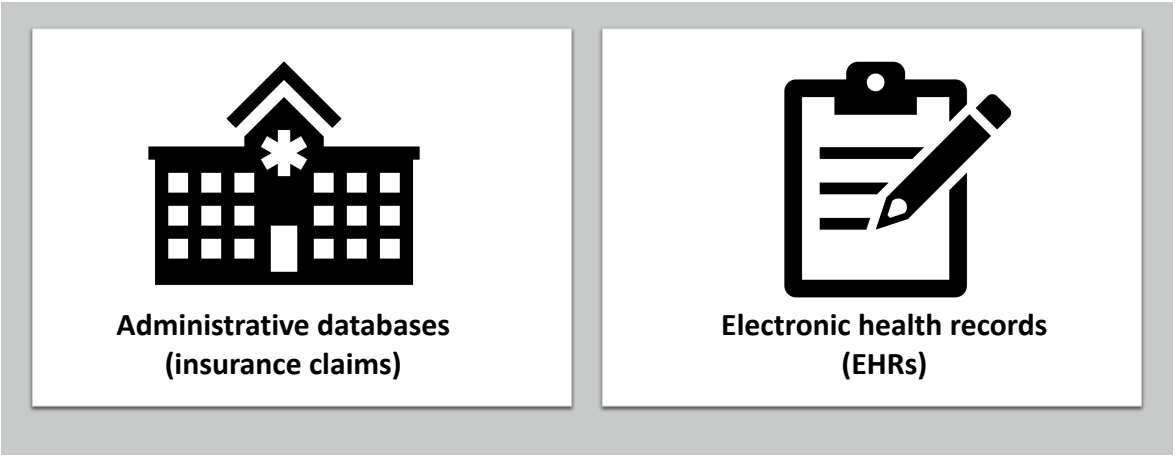
Challenge: sequential analysis of observational data

Sequential Hypothesis Testing



- Sequential multiplicity!
- Standard approach: **MaxSPRT**
- But it's not very good…

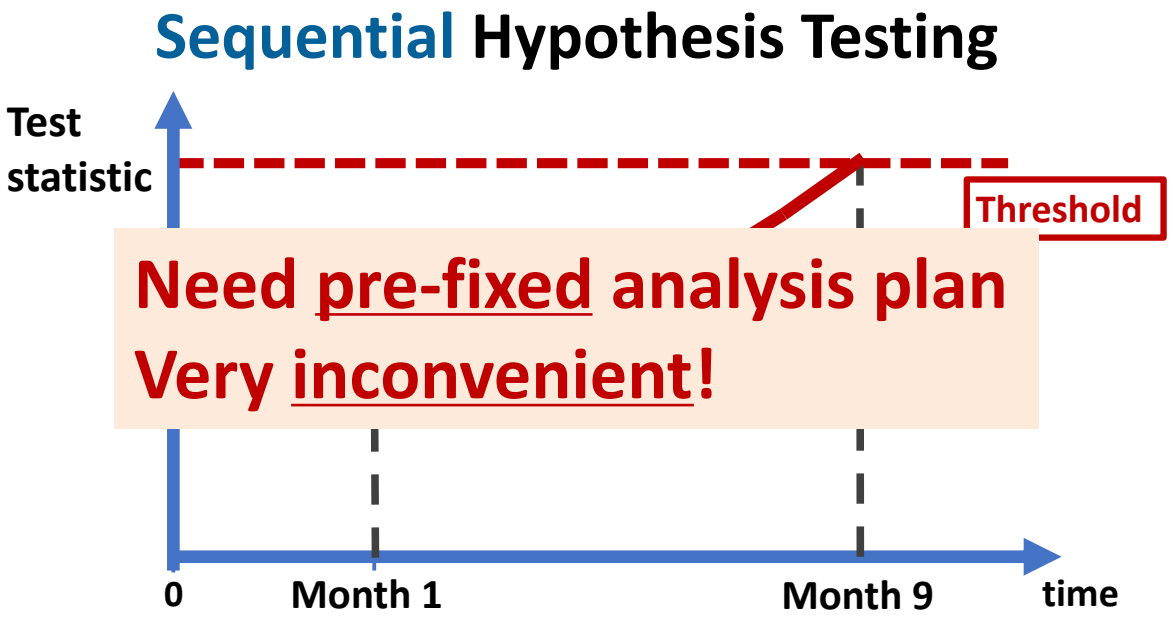
Observational Healthcare Data

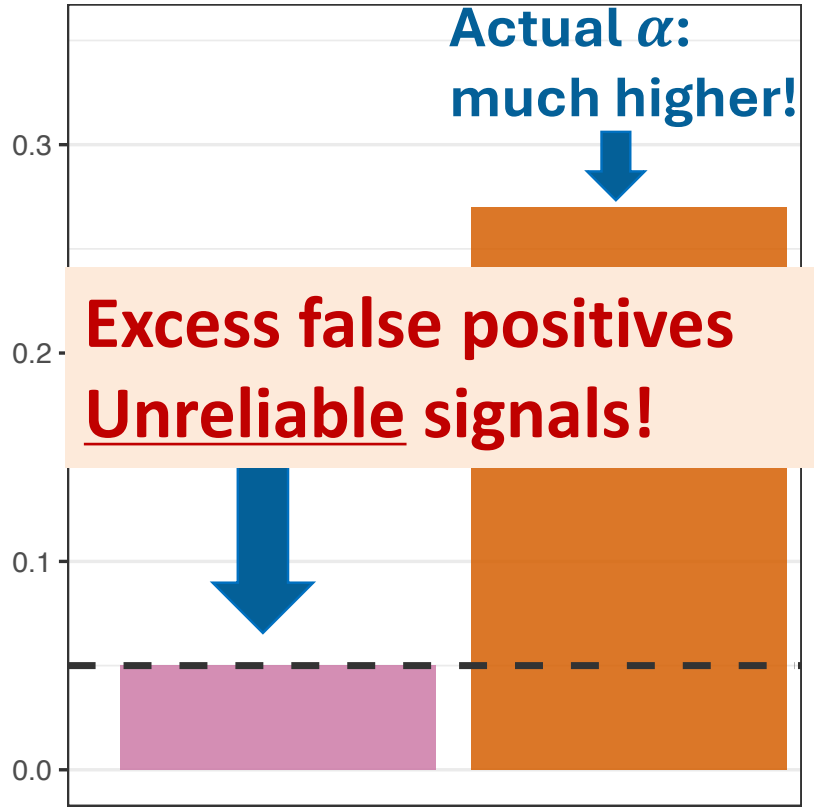


- Bias induced by systematic error
- Hugely inflate test error
- No coherent solution for this!

MaxSPRT: **Max**imum **S**equential **P**robability **R**atio **T**est, by Kulldorff et al., 2011

Challenge: sequential analysis of observational data





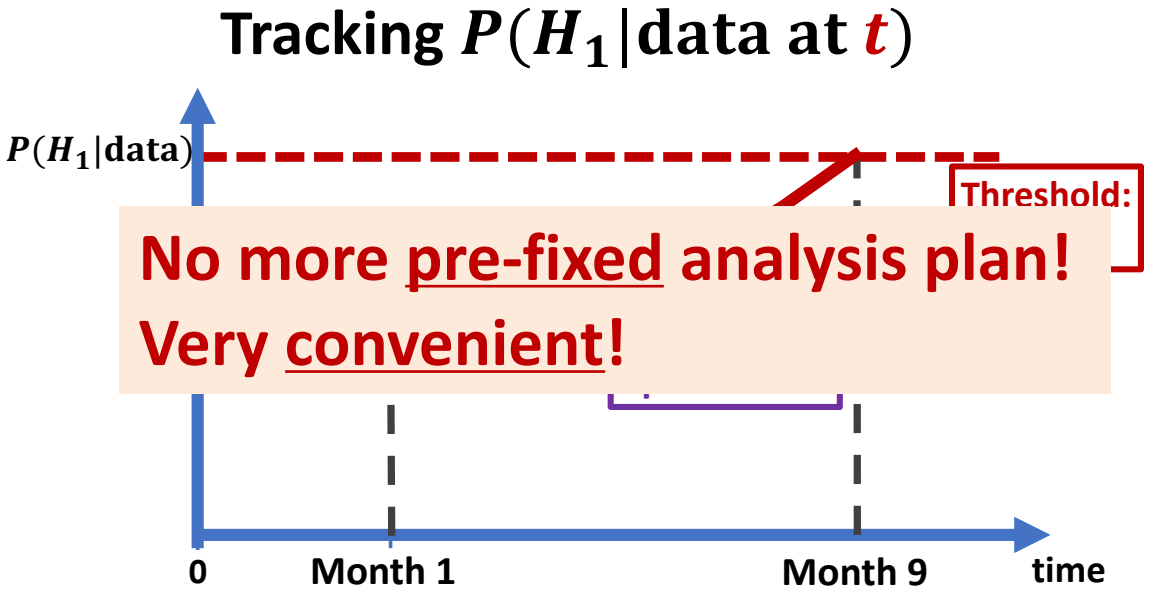
- Sequential multiplicity!
- Standard approach: **MaxSPRT**

Implication: detecting way more vaccine adverse events than truth ☹

MaxSPRT: **Max**imum **S**equential **P**robability **R**atio **T**est, by Kulldorff et al., 2011

Standard approach no good! Our better solution:

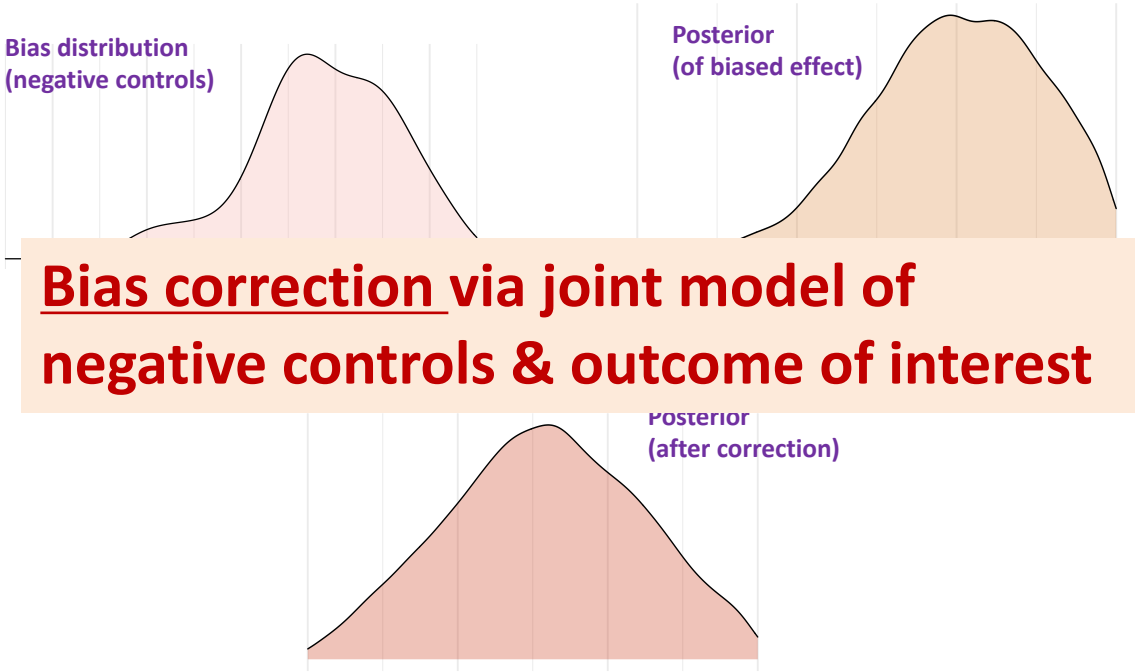
- **More flexible framework!**



No more <u>pre-fixed</u> analysis plan!
Very <u>convenient</u>!

- Bayesian sequential analysis
- posterior probability given accrued data
- more interpretable than p-values

- **Less bias!**

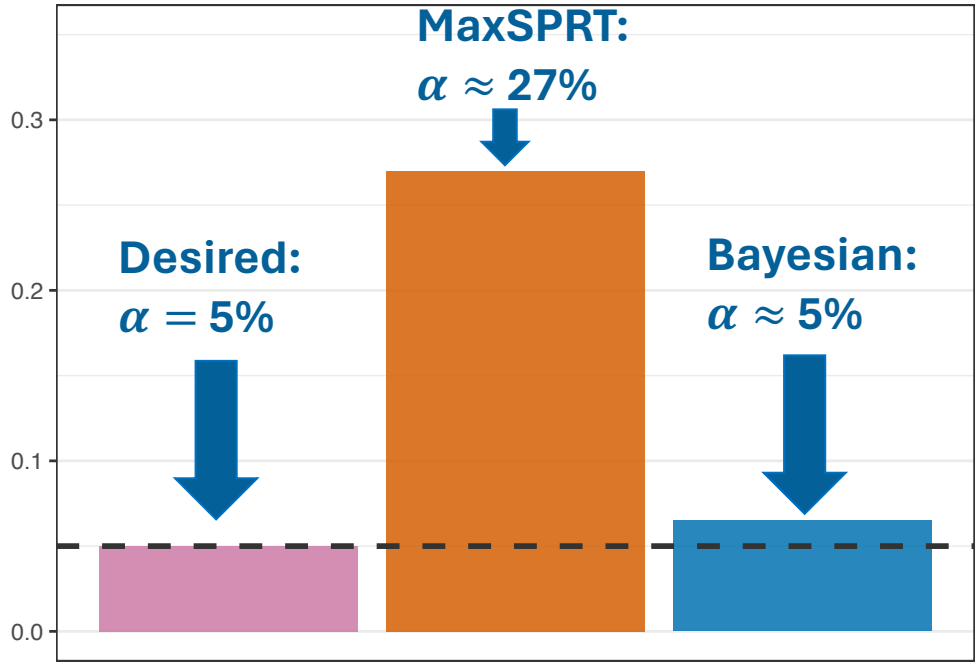


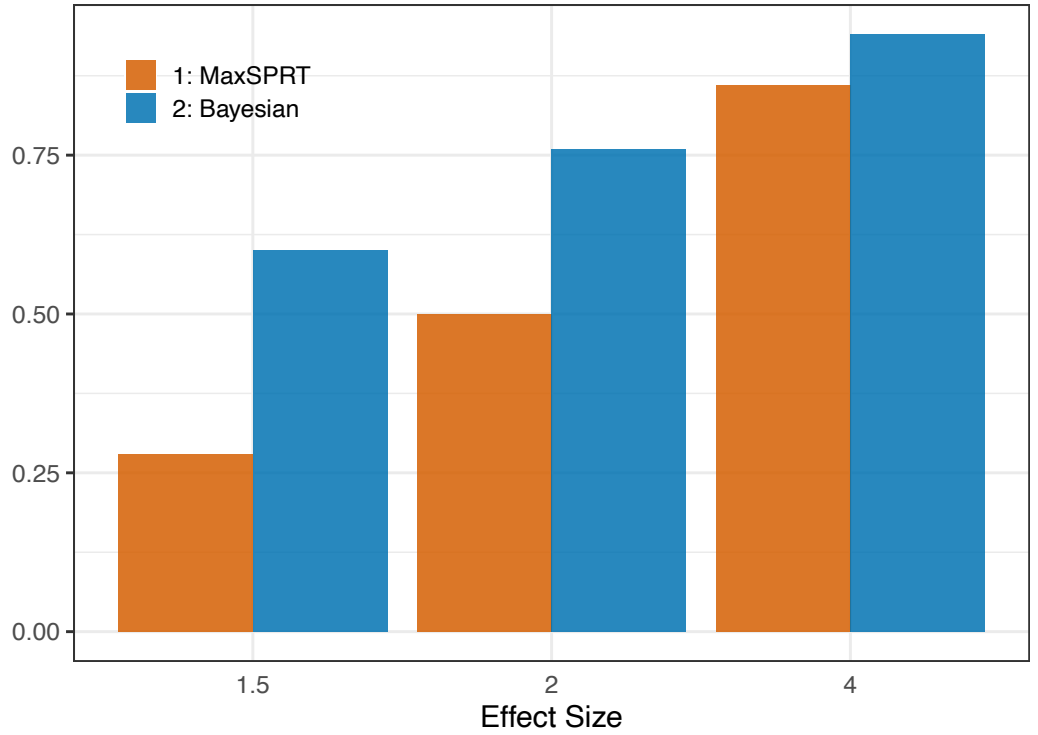
<u>Bias correction</u> via joint model of negative controls & outcome of interest

- Analyzing negative control outcomes
- outcomes w/ null effect → empirical bias distribution

Better method → Improved performance

- Reduced Type 1 error, higher statistical power, faster detection





substantially reduced Type 1 error

more powerful when allowed same Type 1 error

More results and details of empirical evaluation in: Bu et al. 2024, *Stats in Med*.

Resources

- Team (@OHDSI):
  - Thomas Falconer
  - George Hripcsak
  - Kristin Kostka
  - David Madigan
  - Jody-Ann McLeggon
  - Aki Nishimura
  - Patrick Ryan
  - Louisa Smith
  - Martijn Shuemie
  - Marc Suchard
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- Links:
  - Evidence Explorer: **https://data.ohdsi.org/BetterExplorer/**
  - EvidenceSynthesis R package: **https://github.come/OHDSI/evidenceSynthesis**

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