Bayes for Flexibility in Urgent Times

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Big Picture

- Efficacy is not a hypothesis; it is a matter of degree
- Hypothesis testing and associated thresholds have hurt science
- Would you rather know the chance of making an assertion of efficacy when the treatment has no effect, or the chance the treatment is effective?
- Probabilities conditioning backwards in time/information flow are not directly actionable

Problems We Face in COVID-19

- Relatively little known about the virus and its treatment
- Rapid decision making required
- Studies must be launched and concluded quickly
- DSMBs must act on information from other studies
- DSMB meetings cannot be scheduled far in advance
- A data look may be required at any time
- Best to just allow for infinitely many data looks
- See `hbiostat.org/proj/covid19`

High Level View of Statistical Approaches

- Frequentist: probability of data given an assertion is true
- Bayesian: probability assertion is true given the data
- Frequentist type I error: probability of making an assertion of efficacy over the long run of replicate studies like yours **except** that the treatment has zero effect and does no harm
- Bayesian posterior probability of efficacy: probability of true efficacy underlying the process generating **our** data (probability that an assertion of efficacy is true)
- One minus posterior probability of efficacy: probability of no effect or harm (*regulator's regret*)

What is Actionable?

What is Not Actionable

After a patient has a diagnostic test, the sensitivity and specificity of the test

What is Actionable

The probability the patient has the disease

Advantages of Bayes, *continued*

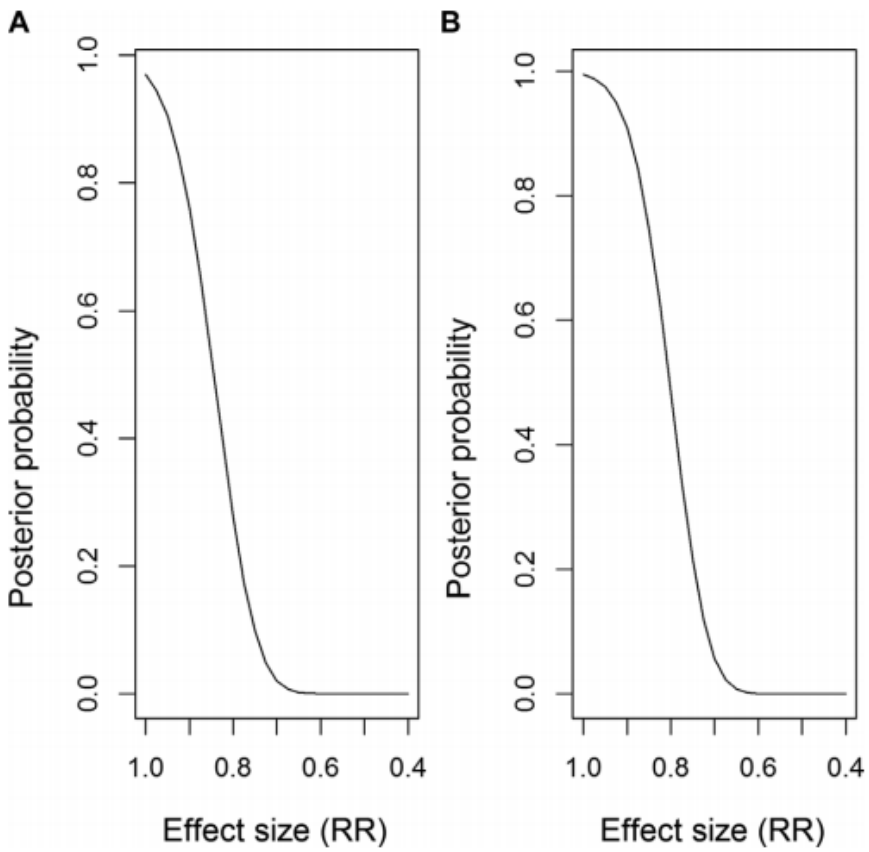


Figure 3 Posterior probability of specified effect sizes, using (A) flat prior, (B) evidence-based priors. The line shows the probability of the relative risk (RR) being lower than the values on the x-axis (ie, a bigger treatment effect). A RR <1 indicates that the primary outcome rate is smaller in the intervention arm compared with the control arm.

EG Ryan et al, *BMJ Open* 2019; 9

Examples of Posterior Probabilities

- Prob(any assertion or combination of assertions)
- Prob(efficacy > 0)
- Prob(efficacy $>$ MCID)
- Prob(non-inferiority)
- Prob(efficacy > 0) on Nov. 2: interpretation completely unaffected by:
- Prob(efficacy > 0) on Nov. 1
- Flexibility:
  Prob(hit any 2 of 4 migraine headache endpoints)

Besides The Interpretation Does It Matter That *p*-values are Backward Probabilities?

- Can't inject appropriate skepticism into the calculation
- Can't inject prior relevant information (skeptical or positive) into the calculation
- Being backwards is the **cause** of multiplicity problems: Multiplicity is caused by the chances you give data to be extreme, **not** from the chances you give assertions to be true
- Being backwards means you have to take into account how the data arose instead of just interpret the data at hand
  - Frequentist approach is cumbersome for flexible sequential designs or adaptive designs

Fully Sequential Trials: Continuous Learning with Unlimited Looks

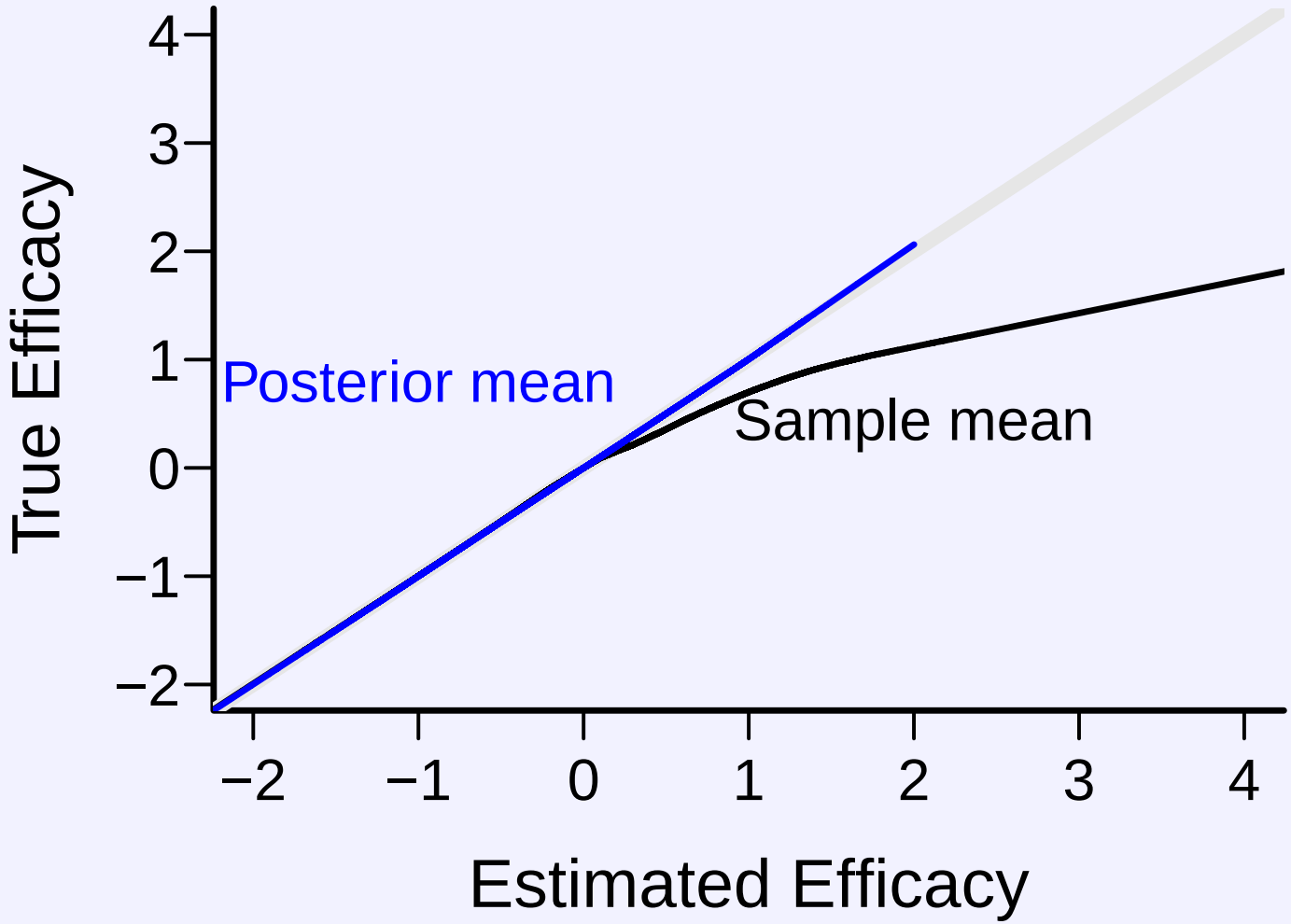
(In a Bayesian analysis) It is entirely appropriate to collect data until a point has been proven or disproven, or until the data collector runs out of time, money, or patience. - Edwards, Lindman, Savage (1963)

- Run 50,000 **different** clinical trials
  (differ on amount of efficacy)
- For each, sample one μ (true efficacy) from the prior
- Generate data ($n = 500$) under this truth
- Do analysis after $1, 2, \ldots, 500$ subjects studied (≤ 500 looks)
- Stop the instant Prob($\mu > 0$) ≥ 0.95 (efficacy) or Prob($\mu < 0.05$) ≥ 0.90 (futility)
- See `fharrell.com` for details and code
- See `hbiostat.org/proj/covid19` for a detailed sequential COVID-19 clinical trial plan

Sequential Testing Simulation, *continued*

- 20393 trials stopped early for efficacy
- 28438 trials stopped early for futility
- 1169 trials went to completion ($n = 500$)
- Average post. prob. of efficacy at stopping for efficacy: 0.961
- Of trials stopped early for efficacy, proportion with $\mu > 0$: 0.960
- Average post. prob. of futility at stopping for futility: 0.920
- Of trials stopped early for futility, proportion with $\mu < 0.05$: 0.923

Calibration of Posterior Mean at Stopping for Efficacy



Advantages of Bayesian Approach

- Computes probabilities on the actionable scale
- Is based solely on basic laws of probability; no special recipes needed
- Is flexible without hurting the science
- Allows experimentation until sufficient evidence
- Use in complex adaptive designs no more complex than use in simple static design
- Can provide simultaneous totality of evidence
- Non-inferiority involves just another posterior probability
- Evidence for non-trivial effects P(E $> \epsilon$)
- P(hitting complex efficacy targets)
- Math for incorporating external information

What is the Greatest Hesitance to Adopting Bayes?

- Fear of not preserving type I assertion probabilities (there is no type I "error")
- Type I assertion probability = long-run P(assertion of efficacy) **if efficacy = 0**
- This probability is **independent of the data**
- Contrast with P(mistake | data) = 1 - posterior P(efficacy)
- Type I error **is not regulator's regret** (approving a drug that doesn't work) but is an assertion probability **assuming the drug doesn't work**
- Analogy:
  - Judging a politician by how often he talks vs.
  - Judging him by how often he tells the truth

New Resource and Discussion Board

- Introductory Bayesian design and analysis course: `hbiostat.org/doc/bayes/course.html`
- Bayesian *t*-tests: `hbiostat.org/doc/bbr.pdf` Chapter 5
- Discussion board for the presentation you are viewing: `bit.ly/datamethods-whybayes`
- `hbiostat.org/proj/covid19`