

Introduction to Bayesian Methods

Workshop

Bayesian Medical Outreach Working Group



Disclosure/Disclaimer

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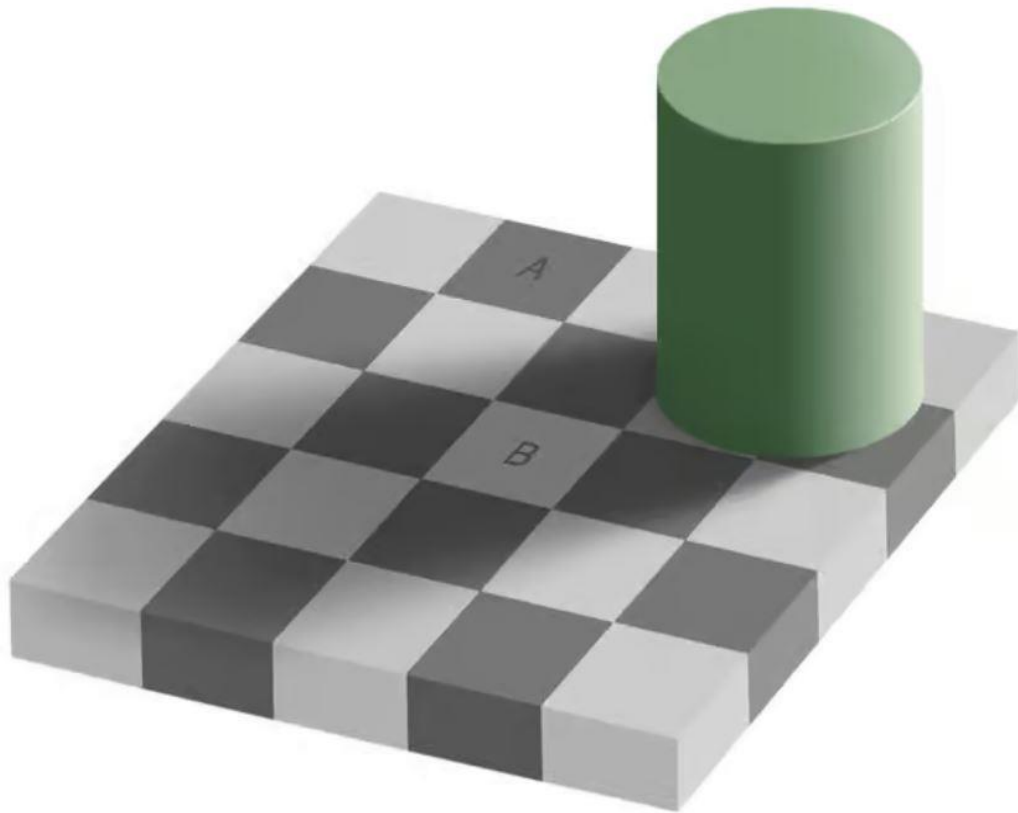
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Eli Lilly, USA
Full-time employee of Eli Lilly

The views presented are the views of the presenter, not necessarily those of Cytel or Eli Lilly.

Motivation to use Bayesian methods

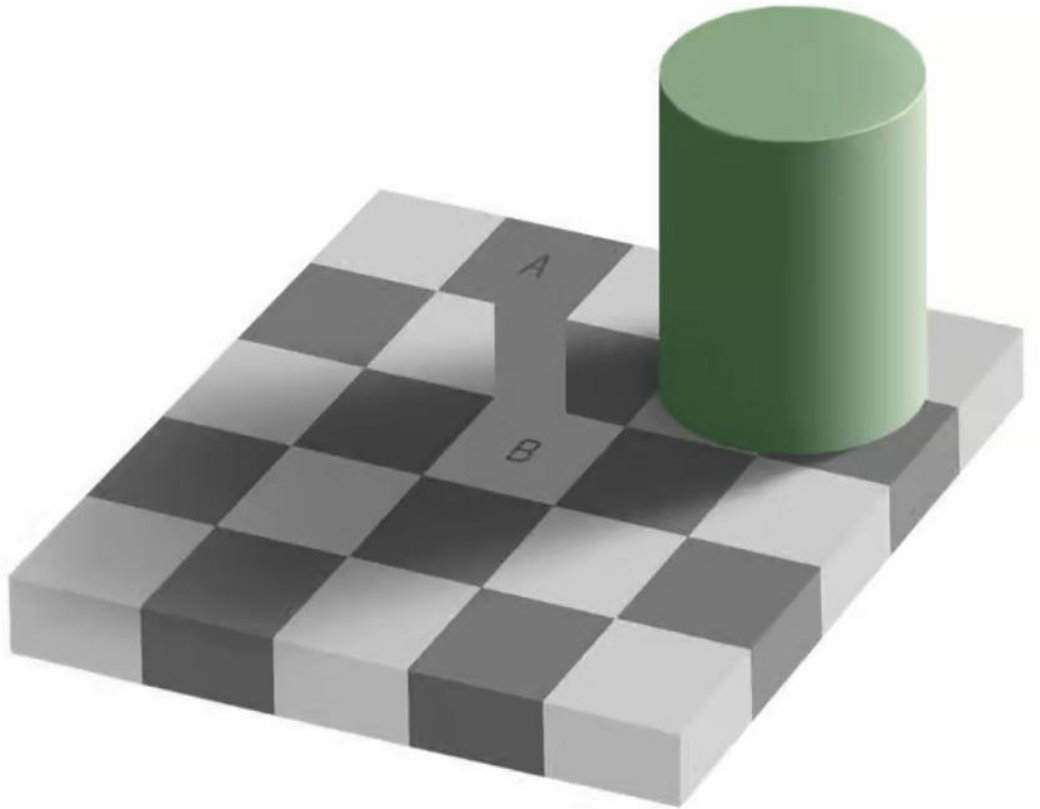
- Directly estimates probability of the treatment effect based on observed data and prior
- Facilitates interpretation for decision-making, e.g. interim futility/adaptations, dose selection
- Allows consistency between missing data imputation (which is Bayesian) and the final analysis
- Allows integration of prior knowledge

Checker shadow illusion



Checker shadow illusion is an optical illusion published by Edward H. Adelson, professor of vision science at MIT, in 1995.^a

Checker shadow illusion



$$P(\text{B} \mid \text{Checkerboard}, \text{Cylinder}, \text{Sun}, \text{Shadow}, \dots) = ?$$

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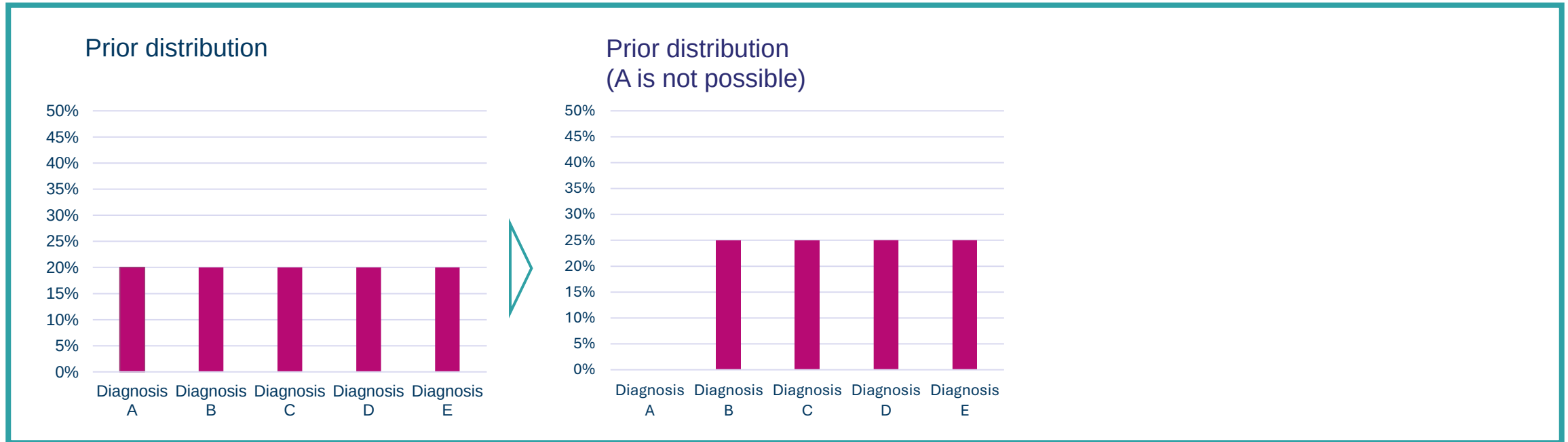
Bayesian naturally aligns with our thought processes

- Bayesian approach starts with prior information; that is the distribution of the parameter of interest



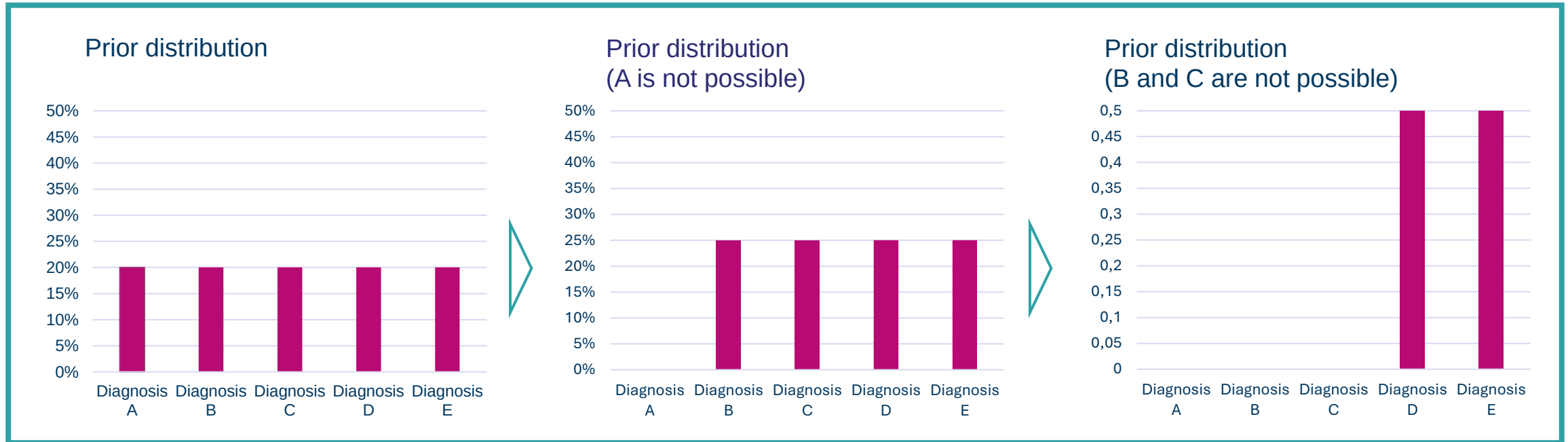
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- Once the data are available this prior information is updated to get the posterior distribution. Inference is carried out using this posterior-distribution of the parameters of interest.



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What is the probability of disease, given test positive?

1. The test for a disease is positive
 2. We know that
 - Test is always positive in those with a disease (sensitivity)
 - 99% of people without a disease test negative (specificity)
 3. What is your patient's chance of having a disease? (PPV)
- => To answer this question, we need prevalence of the disease in the population of interest (prior)

	Test +	Test -
Disease +	100	0
Disease -	1	99

Bayes' rule

$$P(A | B) = \frac{P(B | A) \cdot P(A)}{P(B)}$$

Does it matter?

Frequentist $\Rightarrow \text{pr(Data|H0)}$

Bayesian $\Rightarrow \text{pr(H0|Data)}$

as different as

Pr (test positive | have a disease)

Pr (have a disease | test positive)

The Prosecutor's fallacy: under the assumption of the suspect is innocent, the facts of the case would be incredibly unlikely, and therefore the suspect is unlikely to be innocent

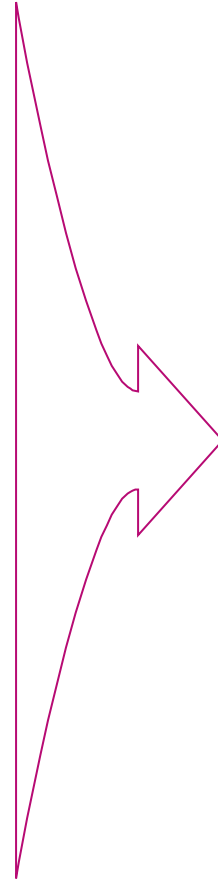
5 min on Prosecutor Fallacy: <https://www.youtube.com/watch?v=E3VoTTR8MXM>

Translating the concept of prior to clinical trial context

- What do we know about the disease and current care?
- What do we know about the investigational therapy?
- What is relevant to our research questions?
- How sure are we?

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- Prior specifies plausible values and the uncertainty of these parameters
- Prior have different degree of informativeness
- Prior distribution represents the information about an uncertain parameter before the data are collected in our trial
- The “strength” of prior can be quantified by Effective Sample Size (ESS)



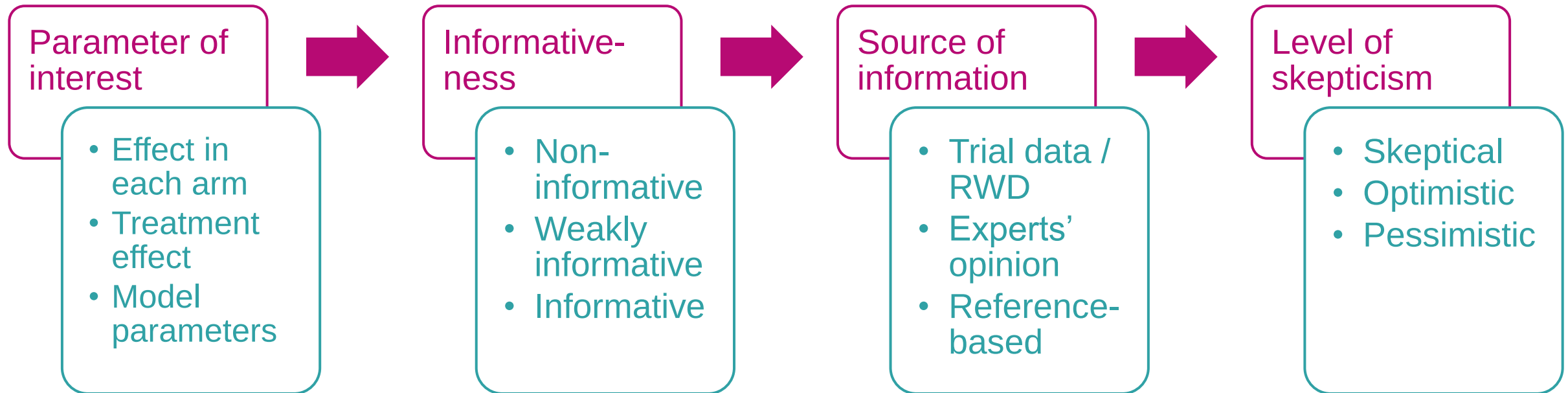
Prior distributions

- ❖ Lack of standardized definitions in the literature
- ❖ Read carefully the definitions authors used



Non-informative *Improper* *Flat*
Optimistic *Vague* *Diffuse* *Weakly informative*
Neutral *Informative* *Sceptical*

Prior distributions: variety of approaches

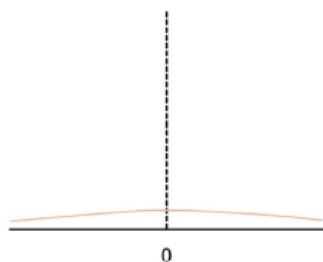


Priors with Extremely Large and Large Uncertainty

Non-informative priors

The posterior will be dominated by the study data (the likelihood)

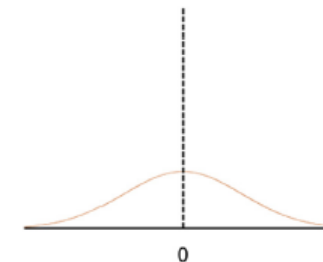
- Represented by very wide distributions
- Contains no information regarding the effect of the intervention under investigation
- Caution: not recommended
 - Often not appropriate as it puts too much prior probability on astronomically high or low effects that are clinically implausible
 - Can lead to implausible posteriors especially in studies with limited sample size (rare diseases)



Also referred to as *Improper*,
Diffuse or *Flat* prior

Weakly informative priors

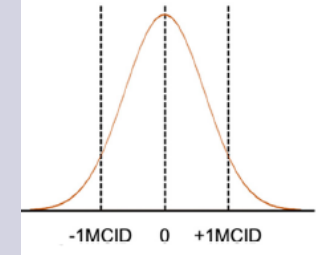
- Have wide distribution that captures clinically plausible values, with limited density on virtually clinically impossible values
- Designed to contain minimal information regarding the effect of the intervention under investigation
- The posterior will be dominated by the study data (the likelihood)



Priors with Large Uncertainty: Reference Priors

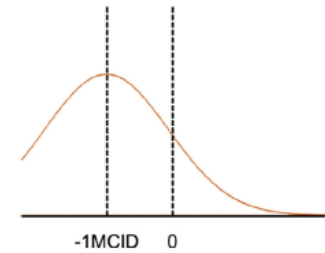
Sceptical priors

- Centred around no effect (e.g. log of OR = 0)
- Assumes small probability (e.g. 10%) that the effect is larger than +1MCID or smaller than -1MCID.



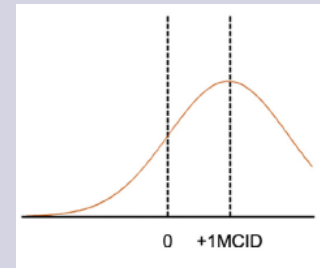
Enthusiastic priors

Centred around the MCID for benefit
The width of the distribution can be chosen such that it reflect desired probability of benefit and harm



Pessimistic priors

- Centred around clinically relevant harm (reversed MCID)
- The width of the distribution can be chosen such that it reflect desired probability of benefit and harm



MCID = minimal clinically important difference

Illustrating Prior Development: Meta-Analysis to construct Prior

Meta-Analytic Predictive (MAP) prior

Robust informative (rMAP) prior is used to handle prior data conflict

$$p_R(\pi_c) = (1 - wR) * \textit{Informative component} + wR * \textit{NonInformative component}$$

Type I and Type II errors are explored by simulations

Borrowing: sources and applications

Borrowing	Source of borrowed data	Bayesian implementation
Borrowing from data external to current trial	Other RCTs, natural history studies, real world data etc. Exchangeability (need comparable subjects and treatment regimens)	External data summarized in the form of informative prior
Borrowing from other treatment arms and periods	Subjects in the same trial randomized previously/concurrently/later to treatments that are similar (but not exactly the same)	Priors and/or models/likelihoods that explicitly model heterogeneity between groups amongst which information is shared

Consideration for exchangeability

Time period

Geography

Diagnosis

Prognosis

Treatments

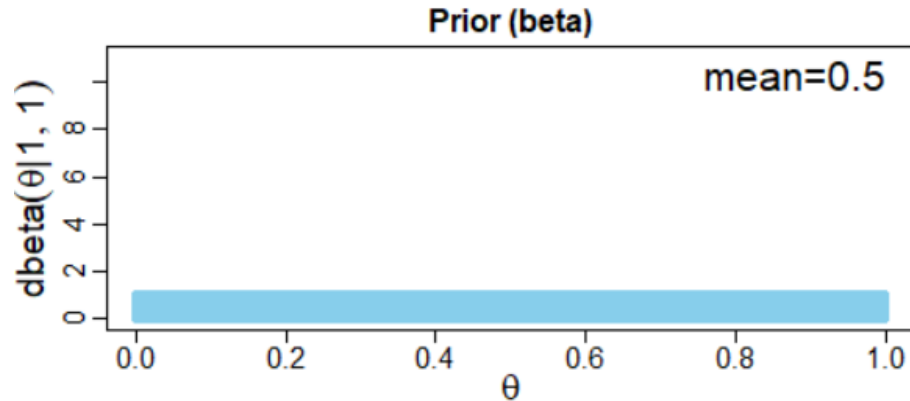
**Other treatment-
related factors**

Follow up period

**Intercurrent
Events**

Outcome

Example of Bayesian Sequential learning



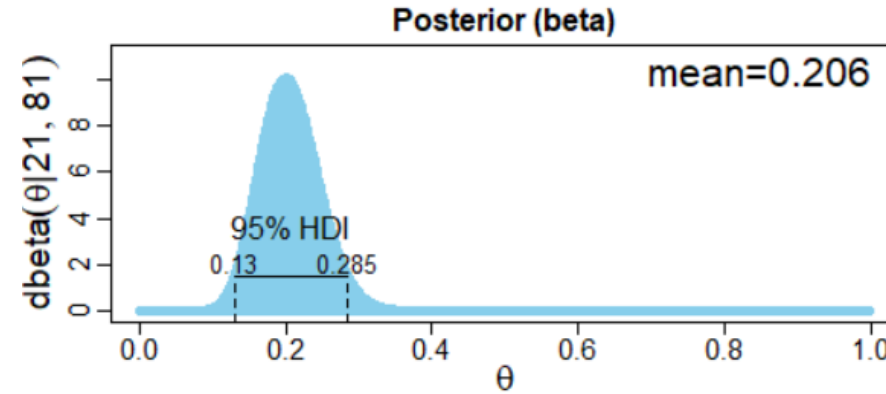
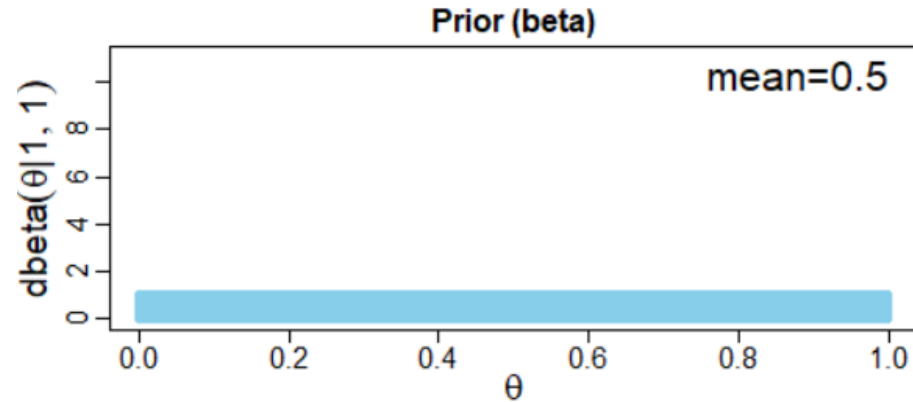
Assuming we study response rate and have no prior information

The primary outcome of interest: response rate (θ)

- Statistically: binary outcome at defined timepoint
- Mathematical description: Bernoulli distribution

No prior information

Example of Bayesian Sequential learning

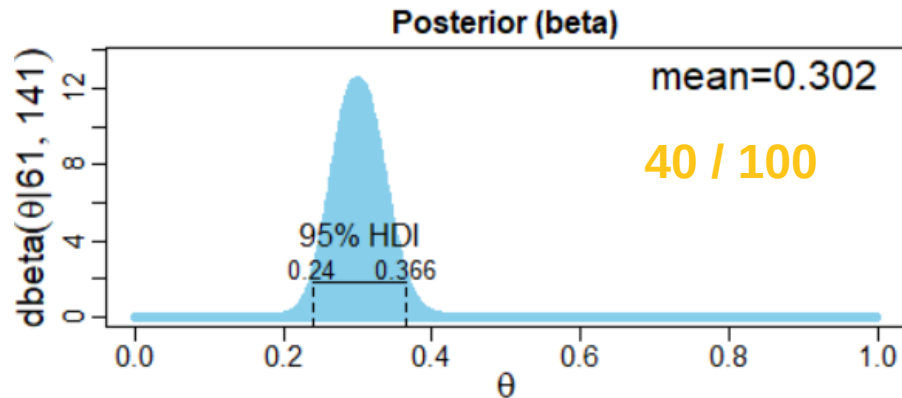
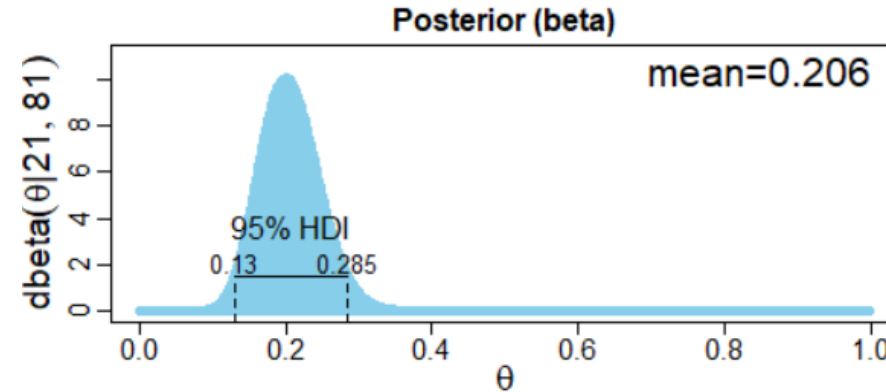
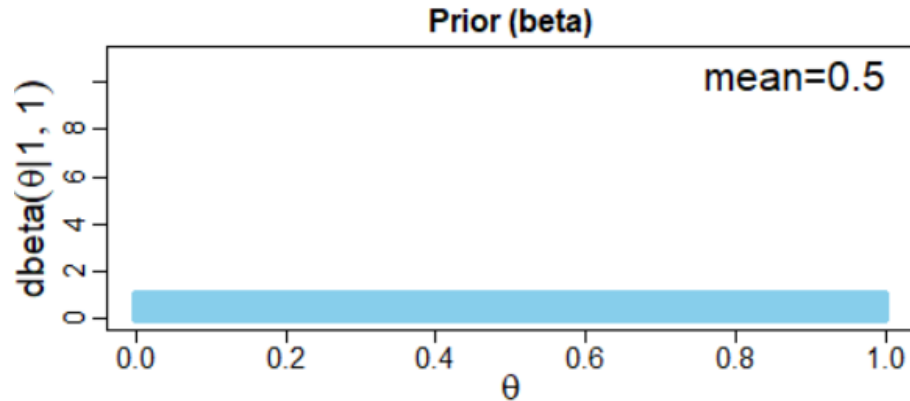


Collected 100 patients' data:
20 responders
80 non-responders

Represents our updated beliefs
about the response rate θ .

HDI : A credible interval (CI) describes the uncertainty of the posterior distribution. The Highest Density Interval (HDI) is a special case of a CI.

Example of Bayesian Sequential learning



Take posterior as the new prior:

Collected 100 additional patients' data:

40 responders

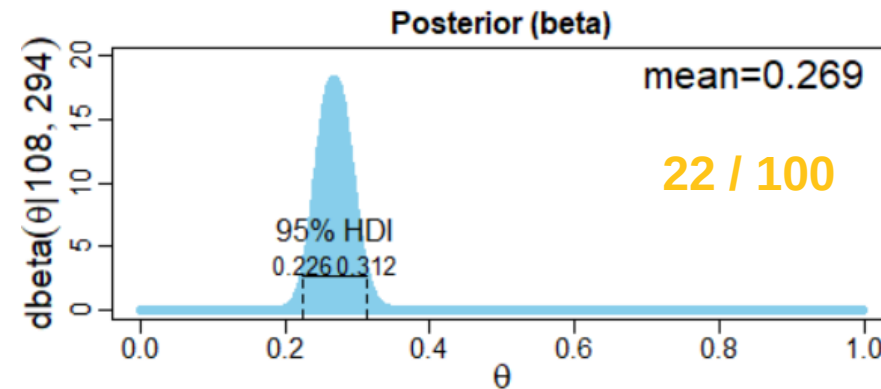
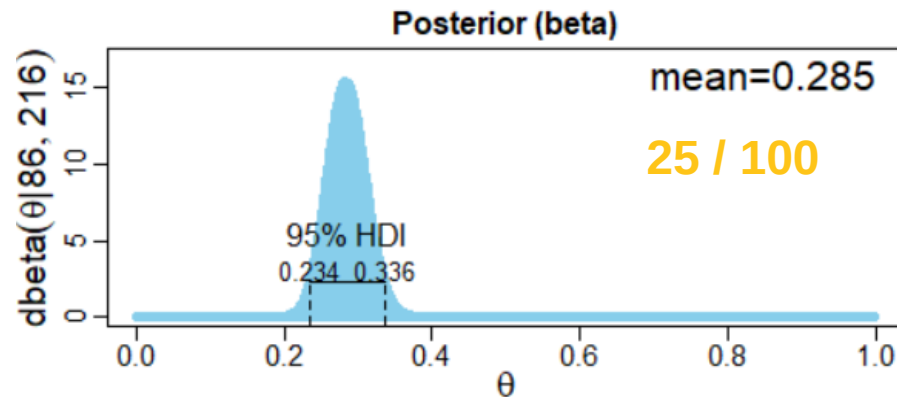
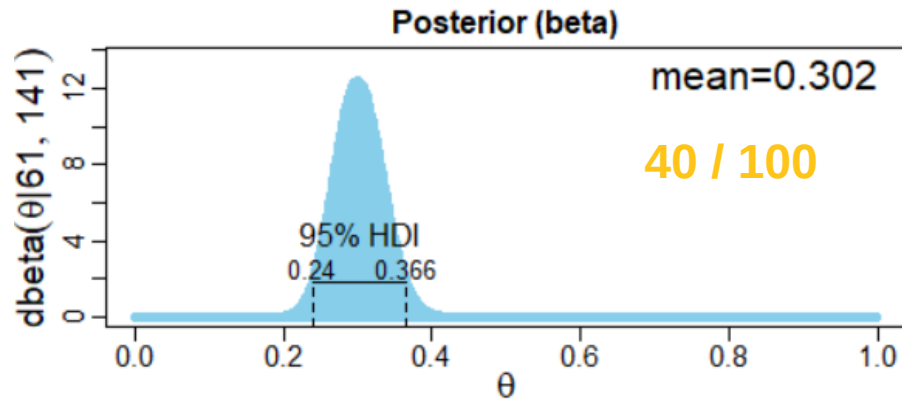
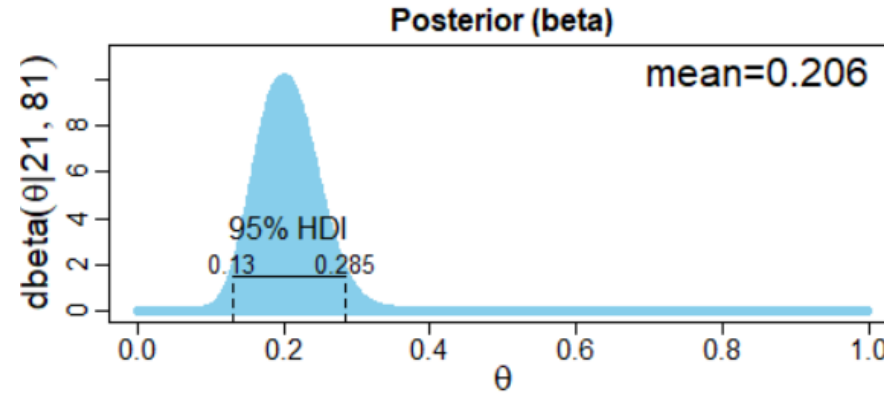
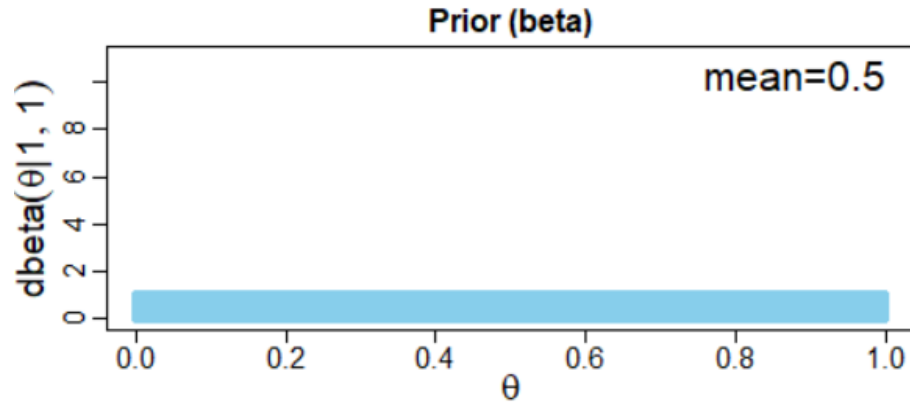
60 non-responders

Overall 200 patients:

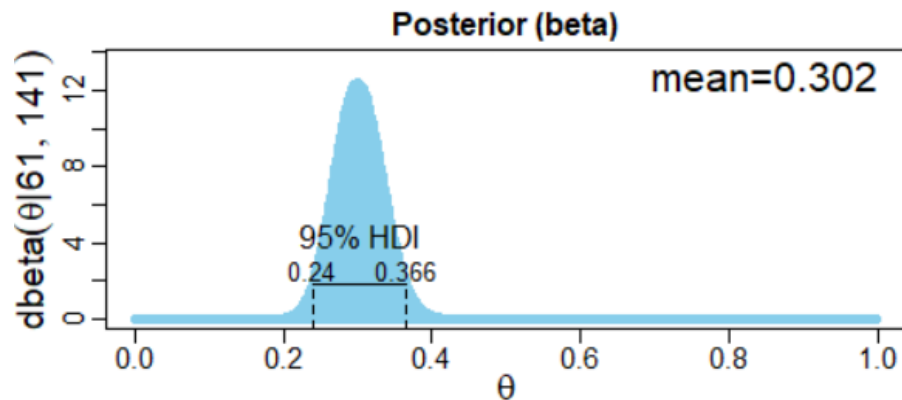
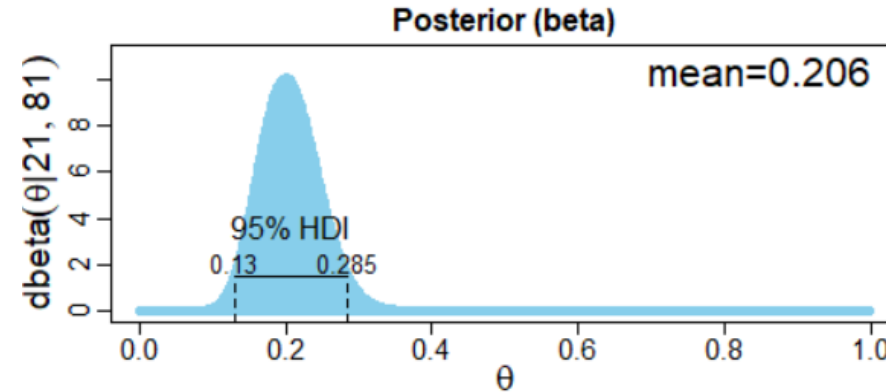
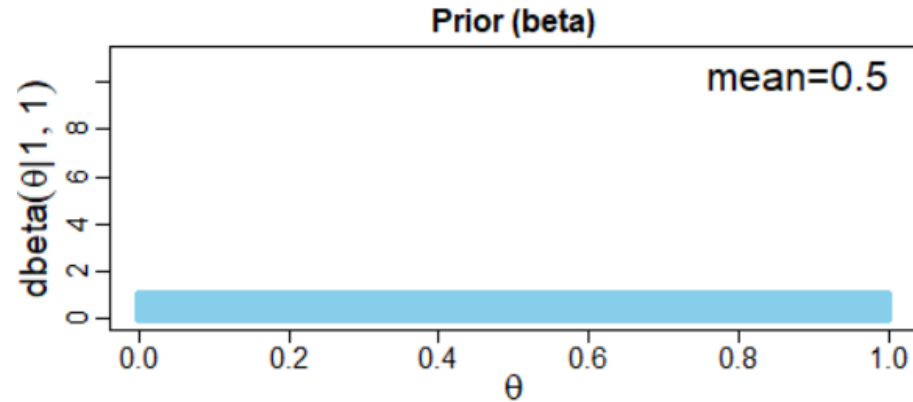
60 responders

140 non-responders

Example of Bayesian Sequential learning

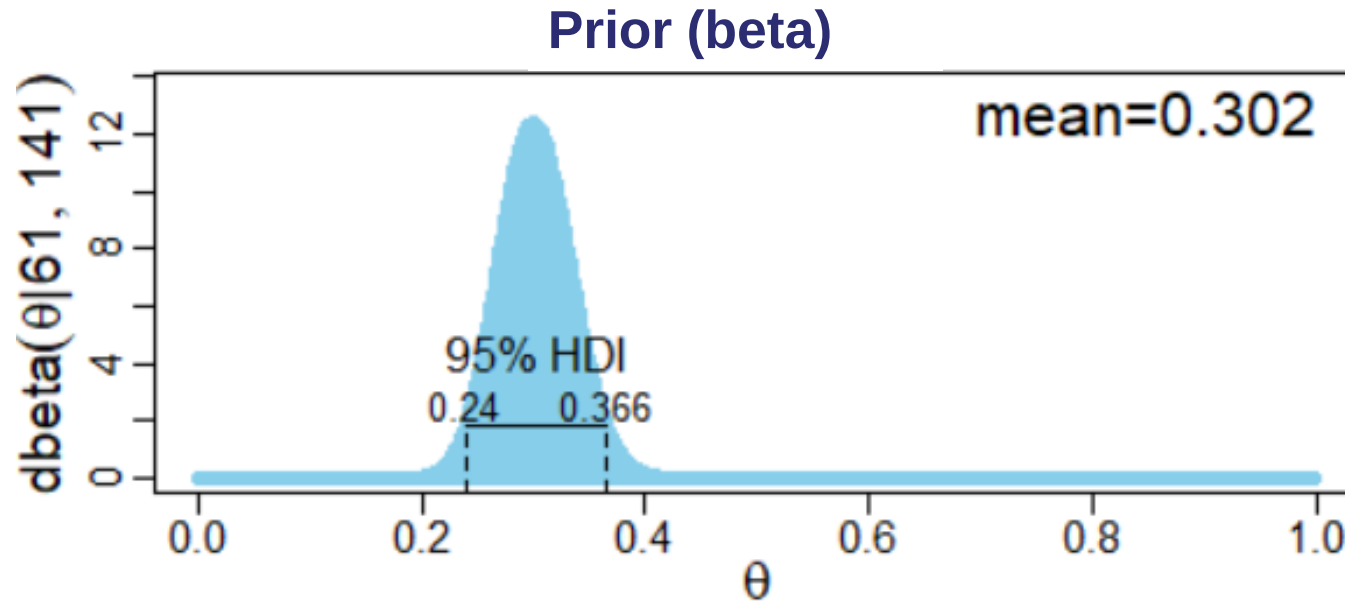


Example of Informative Prior



Assume this is our distribution
prior which is based on $n = 200$

Example of Informative Prior



- Most mass of the prior is in a narrow domain approx. 24% to 37%.
- The prior is based on 202 patient observations
 - Effective Sample Size of Prior = 202
- The “information” of 202 patients is contained in this prior

Inappropriately Informative choice of prior may lead to over-estimation of the treatment effect

- The data are in conflict with the prior distribution
- ▼
- Your study will overestimate the effect of your therapy (Type I error inflation)

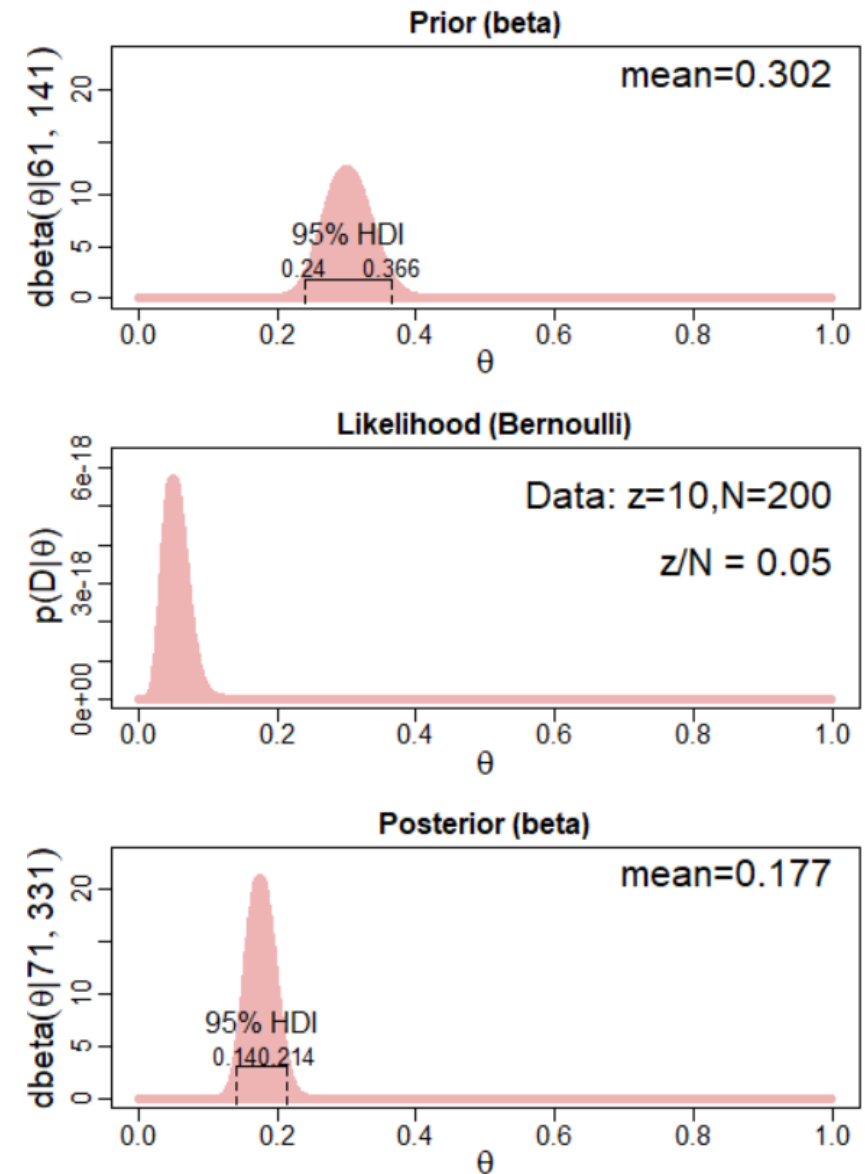
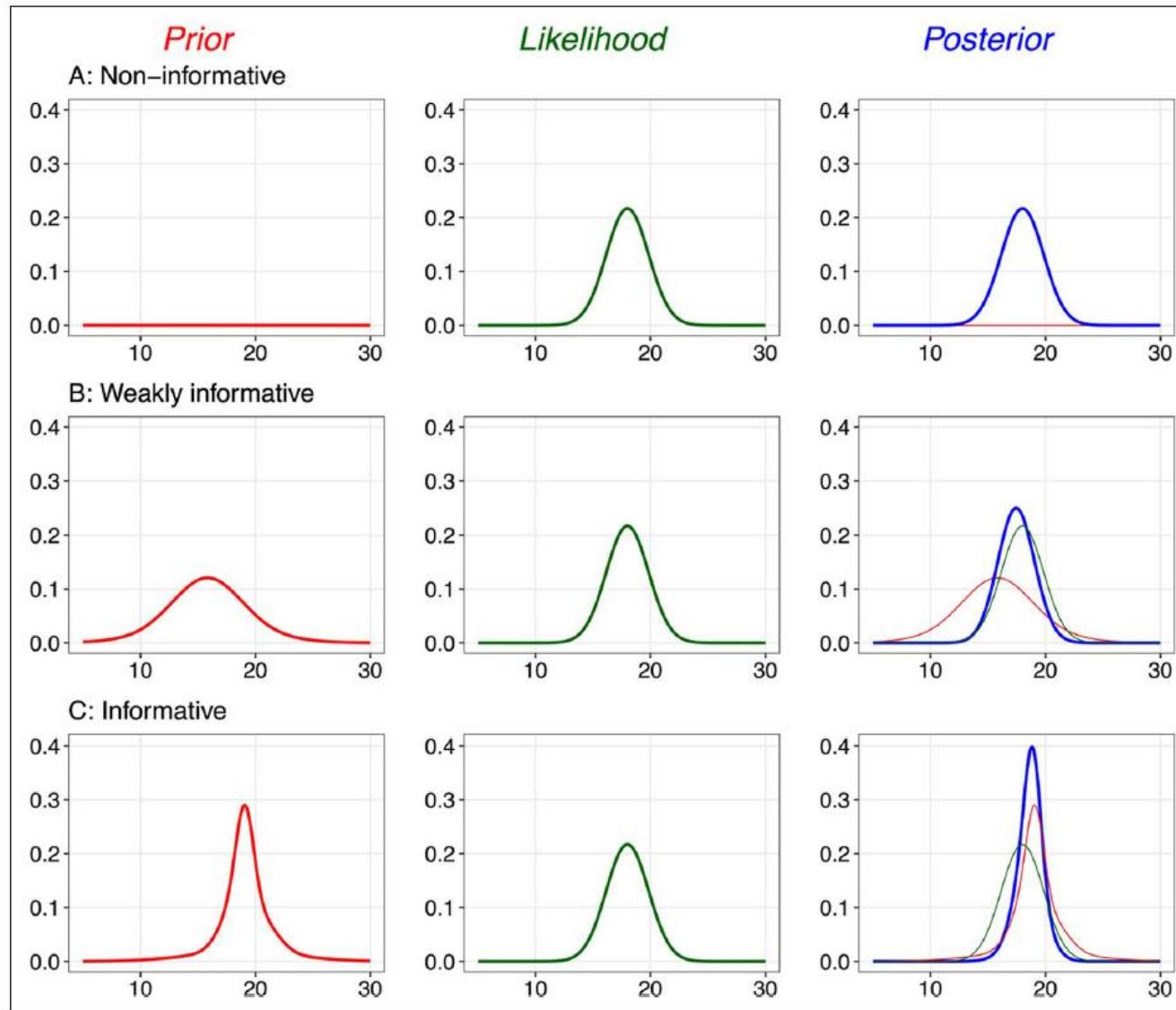


Illustration of Prior's influence on Posterior



Example of Bayesian analysis

Frequentist example

RR (Risk Ratio): 0.76

95% CI: 0.55 – 1.04

p = 0.09

Bayesian example

Prior	Posterior Mean RR (95% CrI)	Posterior Probability that RR is < Specific Threshold (%)			
		RR < 1	RR < 0.9	RR < 0.8	RR < 0.67
Strongly enthusiastic	0.74 (0.57 – 0.95)	99	94	73	22
Moderately enthusiastic	0.78 (0.63 – 0.96)	99	91	61	8
Skeptical	0.84 (0.64 – 1.07)	93	73	39	5
Strongly Skeptical	0.88 (0.71 – 1.09)	88	58	18	0

Goligher E et al. Extracorporeal membrane oxygenation for severe acute respiratory distress syndrome and posterior probability of mortality benefit in a post hoc bayesian analysis of a randomized clinical trial. JAMA. 2018;320(21):2251–9. Zampieri F, Casey J, Shankar-Hari M, Harrell FE, Harhay MO. An overview of theory and example reanalysis of the alveolar recruitment for acute respiratory distress syndrome trial. Am J Respir Crit Care Med. 2021;203:543–52.

Hybrid methods adapted to address clinical question

Continuum of borrowing



Hybrid Bayesian / Frequentist designs

- Bayesian dose selection and final frequentist analysis
- Bayesian IA with final frequentist analysis
- Frequentist for primary and Bayesian for secondary endpoints

How does it help with clinical trials?

Hypothesis testing (binary answer): Frequentist or Bayesian methods

- Reject null (p value)
- Confidence Interval (CI)
- Posterior probability > pre-defined threshold*
- Credible Interval (CrI)

* set to achieve acceptable frequentists Type 1 errors

Quantification of hypothesis (continuum of answers): more interpretable with Bayesian methods

- Dose selection
- Go-no go decision framework
- Interim decisions: prediction questions
- Inform clinical decision on secondary outcomes / subpopulations

Use of prior / external data: Bayesian methods

- Dynamic borrowing
- Platform trials with borrowing