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# Promises and risks of Bayesian analyses in trials of rare diseases

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## “Bayesian Statistics”…
## …and the hope of a magic solution

- Bayesian methods for clinical trials perceived (by some) as being far more efficient than “classical” statistical approaches
- Bayesian methods “take account” of what we already know and build on them; classical statistical methods look at each experiment in isolation

**"Bayesian Statistics"…**
**What do people claim?**
***(after Rich Simon, Jan 2009)***

- Bayesian methods…
  - Require smaller sample sizes
  - Require less planning
  - Are preferable for most problems in clinical trials
  - Have been limited by computing problems

- **Instead: "B ayesian S tatistics"**

## “Bayesian Statistics”… What’s it *really* all about?

- We write down (in some formal way) what we believe about a treatment *before* we do an experiment (e.g. a clinical trial)
  - The *prior*
- Then we do our trial
  - And collect data
- Then we “update” what we *now* believe about the treatment
  - The *posterior*

# Thomas Bayes
# Who was he?

- Thomas Bayes
  - Born 1701 (or 1702???), London
  - Died 1761, Tunbridge Wells, England

# Thomas Bayes
# What's he most famous for?

- "An Essay Towards Solving a Problem in the Doctrine of Chances" *Philosophical Transactions of the Royal Society of London*, 1763;**53**:370–418.

# Thomas Bayes
# What' s he most famous for?

LII. *An Eſſay towards ſolving a Problem in the Doctrine of Chances. By the late Rev. Mr.* Bayes, *F. R. S. communicated by Mr.* Price, *in a Letter to* John Canton, *A. M. F. R. S.*

Dear Sir,

Read Dec. 23, 1763.

I Now ſend you an eſſay which I have found among the papers of our deceaſed friend Mr. Bayes, and which, in my opinion, has great merit, and well deſerves to be preſerved.

# Richard Price's covering letter…

"I am sensible that your time is so much taken up that I cannot reasonably expect that you should minutely examine every part of what I now send you. Some of the calculations, particularly in the Appendix, no-one can make without a good deal of labour…"



rule, is $\frac{1}{n+1} \times E$ into the difference between $\frac{X^{p+1}}{p+1} - \frac{qX^{p+2}}{p+2}$ and $\frac{x^{p+1}}{p+1} - \frac{qx^{p+2}}{p+2} = 12 \times 11$

$$\times \frac{\overline{\tfrac{11}{12}}|^{11}}{11} - \frac{\overline{\tfrac{11}{12}}|^{12}}{12} - \frac{\overline{\tfrac{9}{10}}|^{11}}{11} - \frac{\overline{\tfrac{9}{10}}|^{12}}{12} = .07699$$

&c. There would therefore be an odds of about 923 to 76, or nearly 12 to 1 *againſt* his being right. Had he gueſſed only in general that there were leſs than 9 blanks to a prize, there would have been a probability of his being right equal to .6589, or the odds of 65 to 34.

Again, ſuppoſe that he has heard 20 *blanks* drawn and 2 *prizes*; what chance will he have for being right if he makes the ſame gueſs?

Here X and $x$ being the ſame, we have $n = 22$, $p = 20$, $q = 2$, $E = 231$, and the required chance equal to $\frac{1}{n+1} \times E \times \frac{X^{p+1}}{p+1} - \frac{qX^{p+2}}{p+2} + q \times \frac{q-1}{2} \times \frac{X^{p+3}}{p+3}$

$$- \frac{x^{p+1}}{p+1} - \frac{qx^{p+2}}{p+2} + q \times \frac{q-1}{2} \times \frac{x^{p+3}}{p+3} = .10843 \text{ \&c.}$$

He will, therefore, have a better chance for being right than in the former inſtance, the odds againſt him now being 892 to 108 or about 9 to 1. But ſhould he only gueſs in general, as before, that there were leſs than 9 blanks to a prize, his chance for being right will be worſe; for inſtead of .6589 or an odds of near two to one, it will be .584, or an odds of 584 to 415.

Suppoſe,

# John Holland (*J Roy Stat Soc*, 1962)

"…Thomas Bayes's paper 'An Essay Towards Solving a Problem in the Doctrine of Chances' (1763), … it ranks as one of the most famous, least understood, and controversial contributions in the history of science."

## An example
## A single arm trial for a promising new anti-cancer compound

- The "classical" approach
  1. Decide on sample size (let's assume *n*=30)
  2. Treat these (30) patients
  3. Count the number of responders (let's say 6)
  4. Estimate response rate = 6/30 or 20%
  5. 95% confidence interval 7.7% to 38.6%

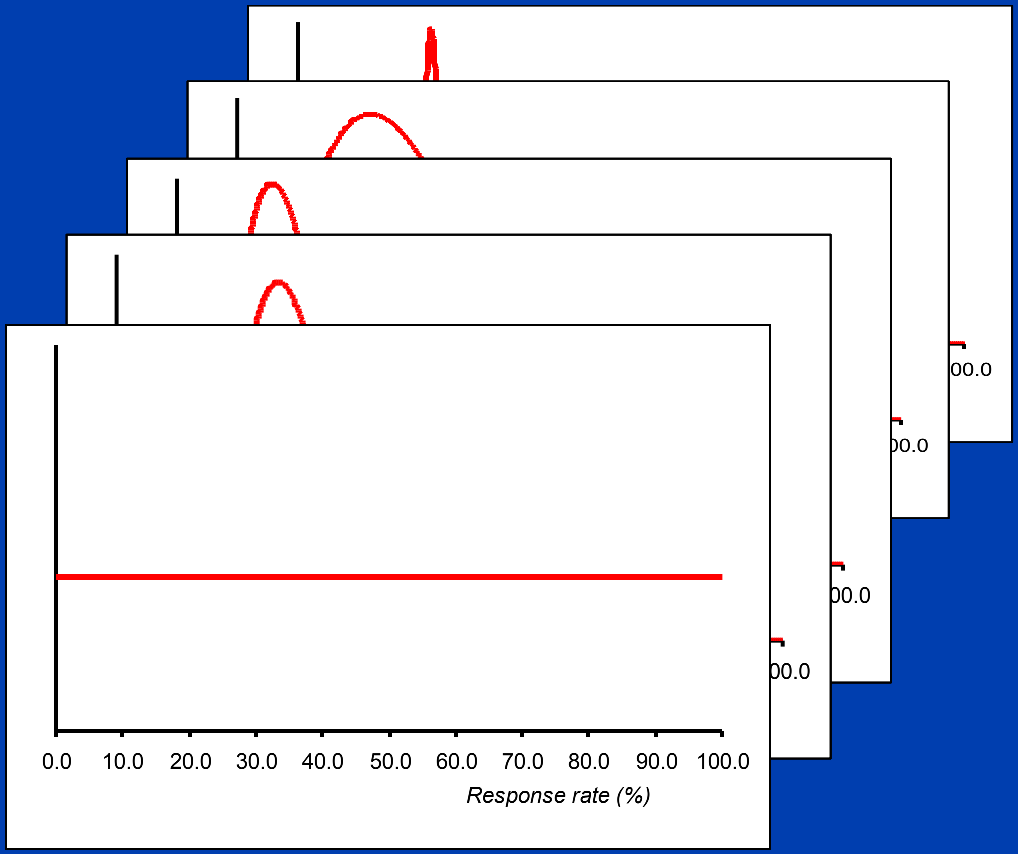
**An example**
**A single arm trial for a promising new anti-cancer compound**

- The Bayesian approach
  1. Set out what we already believe (prior)
  2. Decide on sample size (let' s assume $n$=30)
  3. Treat these (30) patients
  4. Count the number of responders (let' s say 6)
  5. Update what we now believe (posterior)
     - Posterior probability
     - 95% (credible) interval

## Set out what we already know

**We have some prior data suggesting the response rate might be about 20%**

- And I’m really convinced
- Or I’m a fairly unsure
- I’m a sceptic (15%)
- I’m an optimist (25%)
- Actually, I haven’t really got a clue



# Set out what we already know

## We have some prior data suggesting the response rate might be about 20%

- And I’m really convinced
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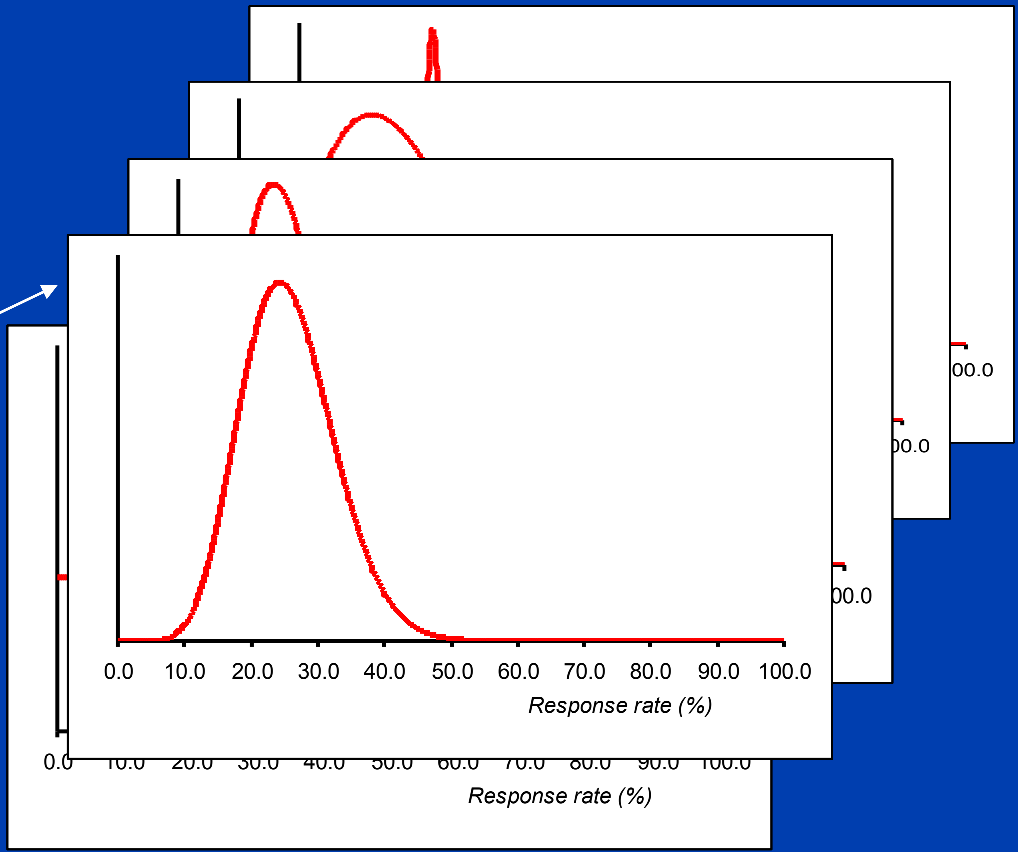
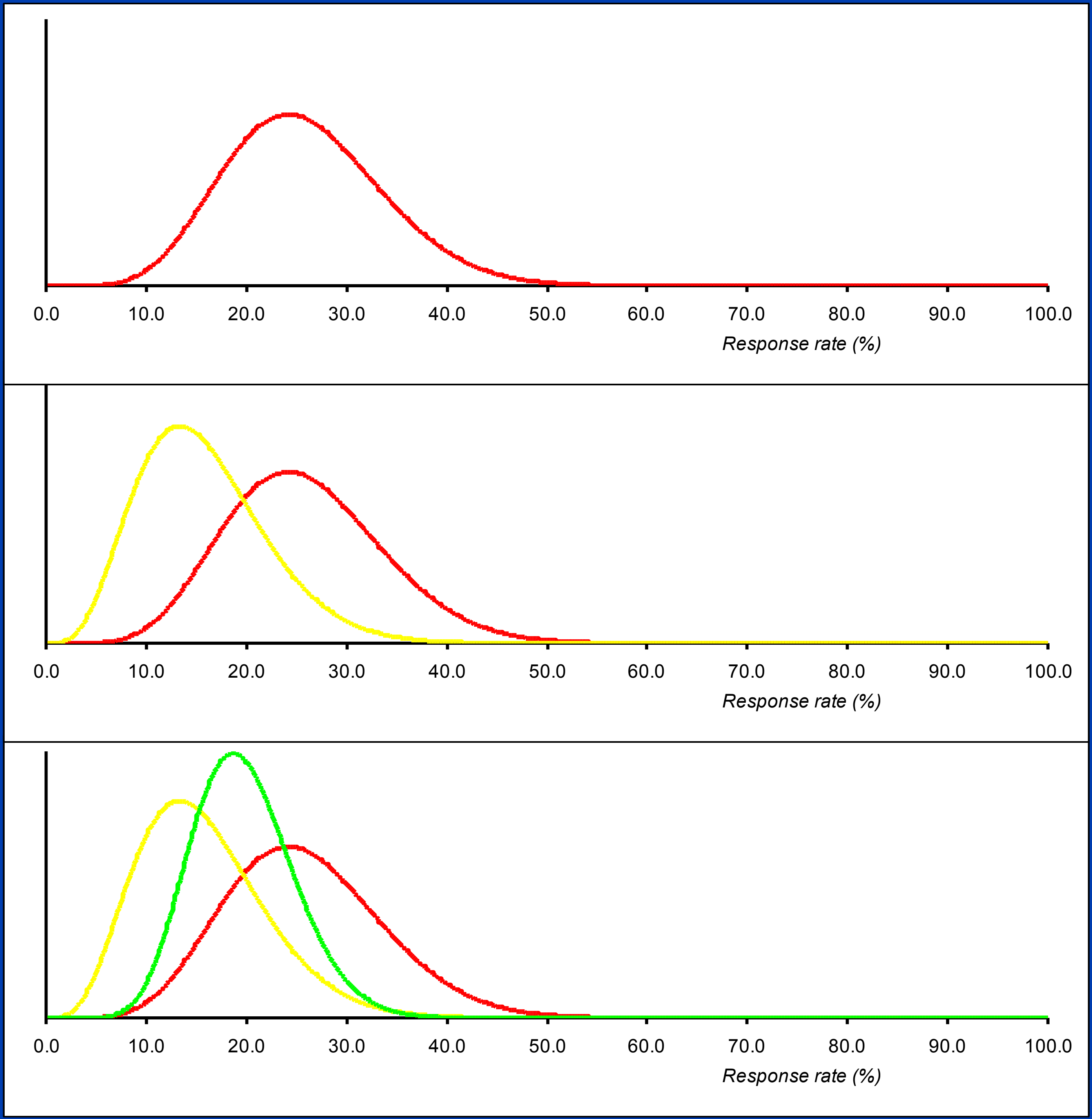


**Decide on sample size**

**This may be exactly the same "classical" trial**

**(let's assume *n*=30)**

- We recruit and treat 30 patients
- We see 4 of them "respond"
- So I used to believe 25% was what I'd expect; now I have data suggesting it's only 13%
- I combine these two (25% and 13%) together…




The prior

The prior

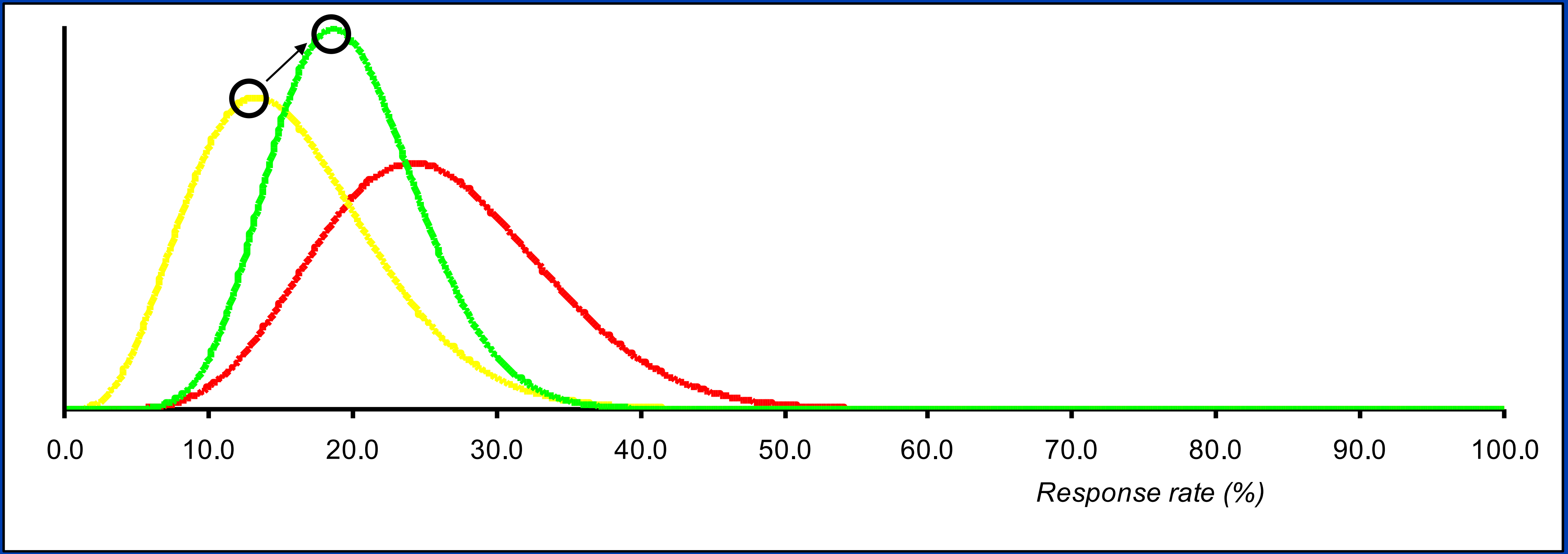
The data

The prior

The data

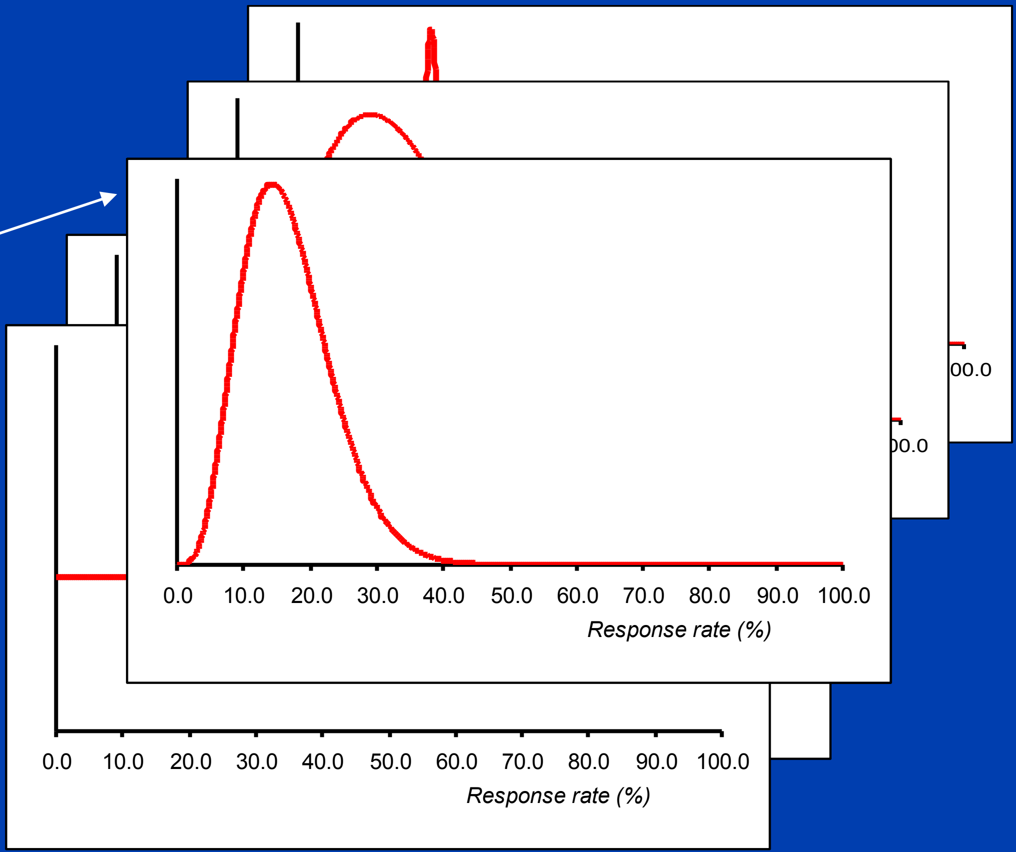
The posterior

# The prior (at 25%) has "rescued" a trial that showed poor results (13%)



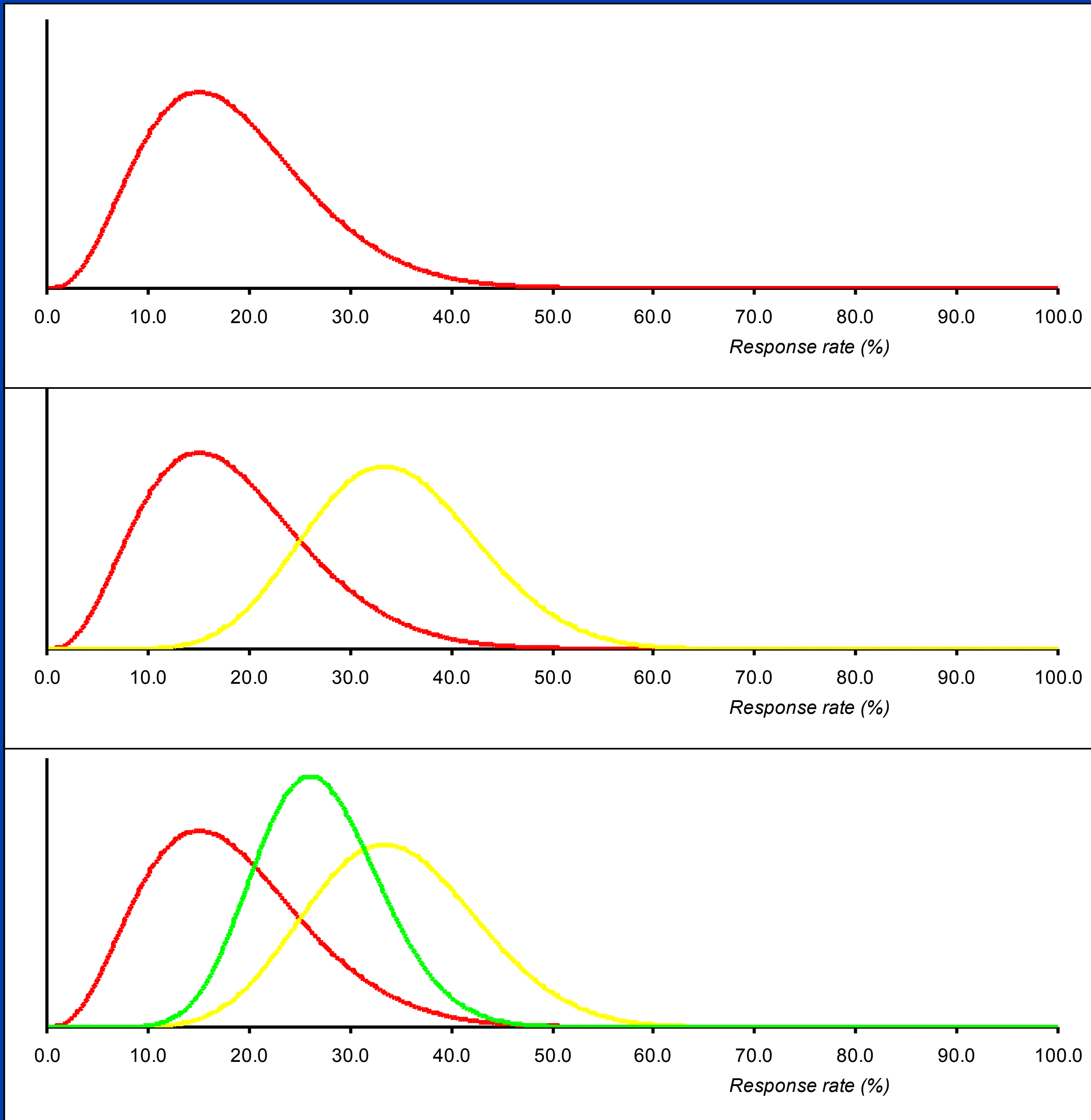
# But let’s look at another example…

- And I’m really convinced
- Or I’m a fairly unsure
- I’m a sceptic (15%)
- I’m an optimist (25%)
- Actually, I haven’t really got a clue



## We do the same experiment

- We recruit and treat 30 patients
- This time we see 10 of them “respond”
- So I used to believe 15% was what I’d expect; now I have data suggesting it’s as good as 33%
- I combine these two (15% and 33%) together…




**The prior**

**The prior**

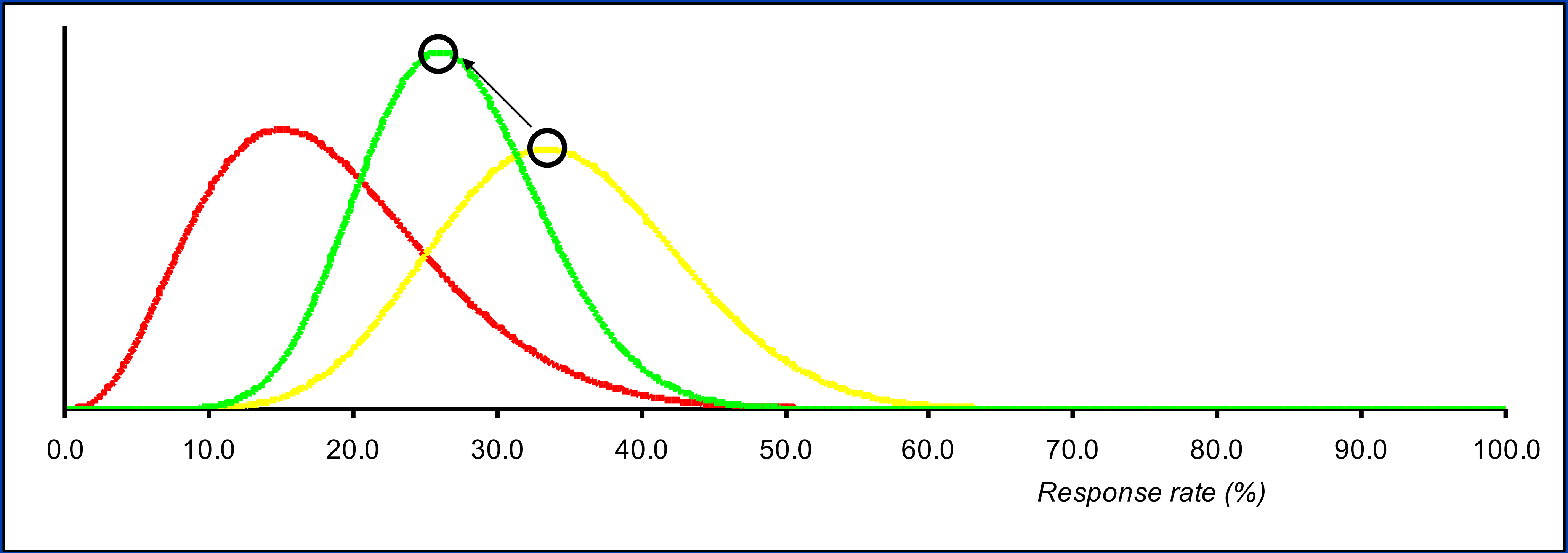
**The data**

**The prior**

**The data**

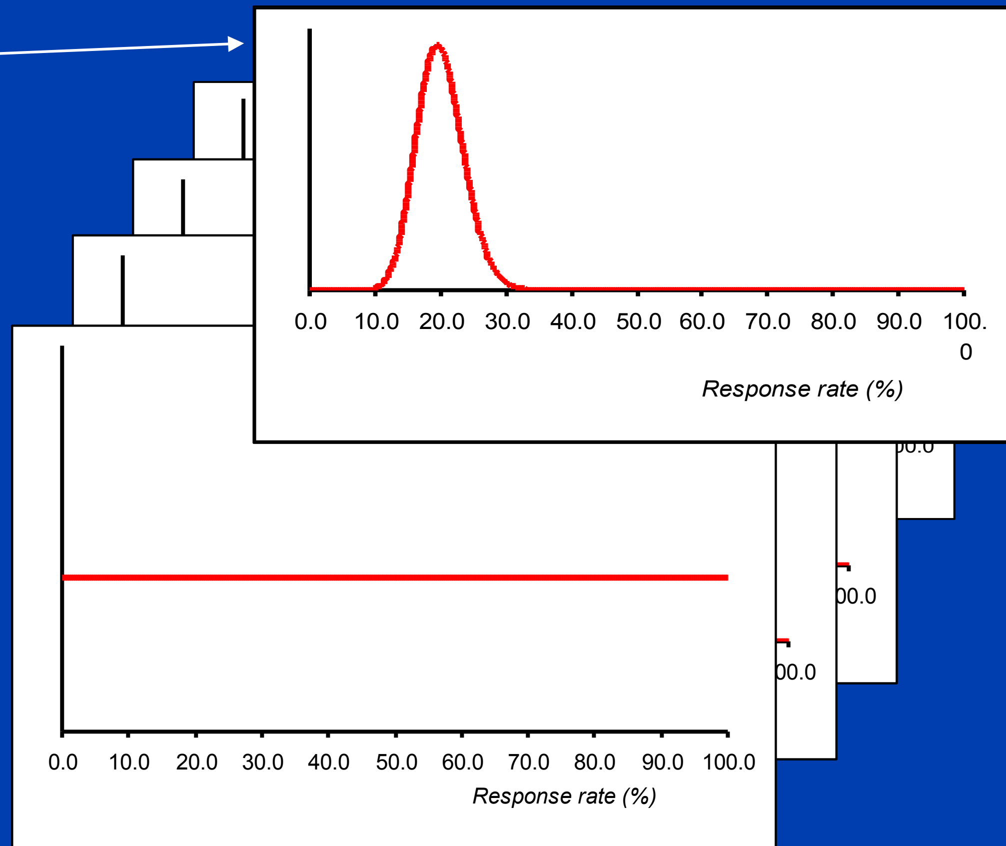
**The posterior**

# Now the prior (at 15%) has “killed” a trial that showed good results (25%)



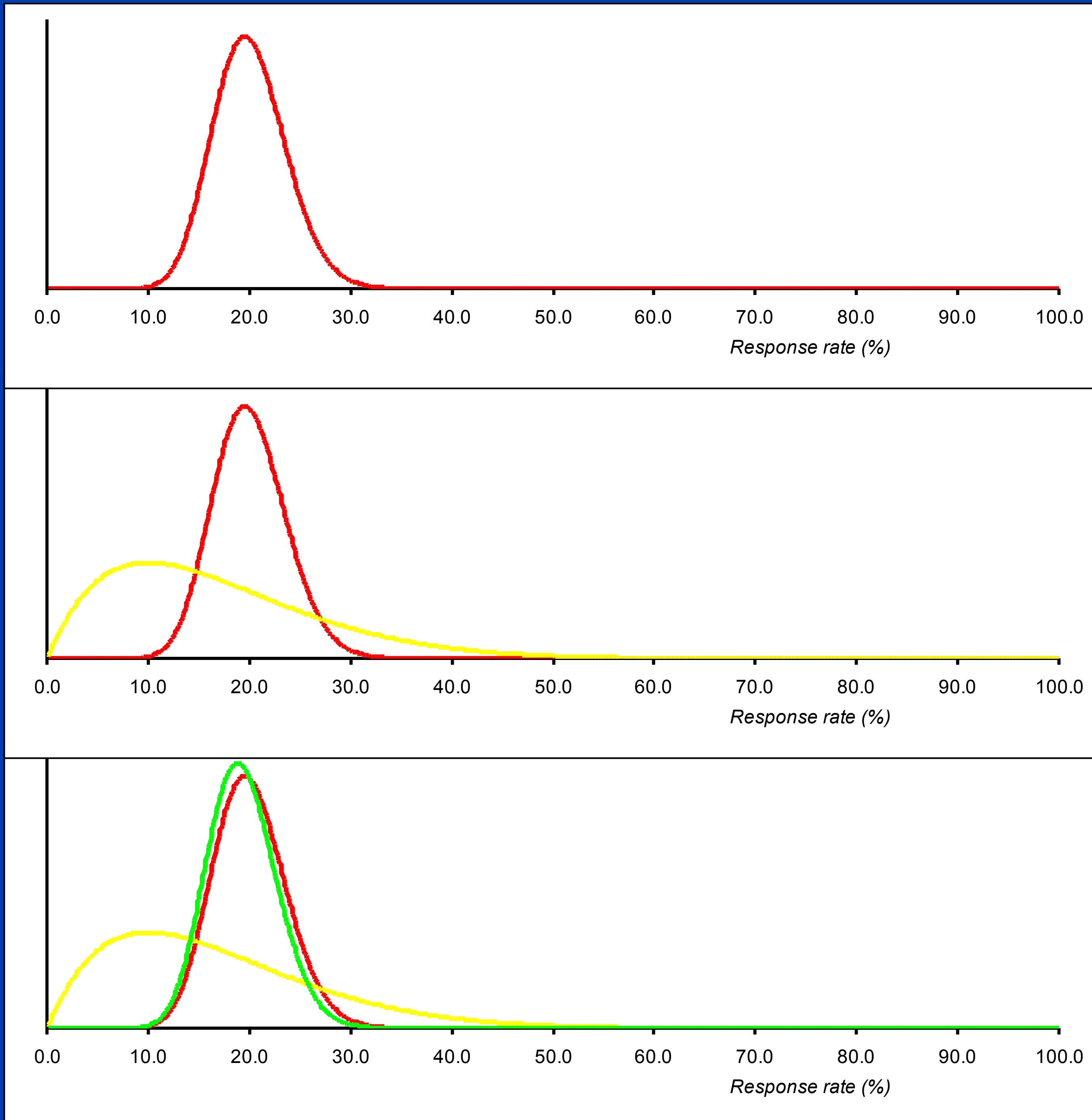
# Worst of all, we can abuse the system…

- And I' m ~~really~~ reasonably convinced
- Or I' m a fairly unsure
- I' m a sceptic (15%)
- I' m an optimist (25%)
- Actually, I haven' t really got a clue



# We do a tiny “experiment”

- We recruit and treat 10 patients
- We see 1 of them “respond”
- So I used to believe 20% was what I’d expect; now I have data suggesting it’s only 10%
- I combine these two (20% and 10%) together…




Roche

The prior

The prior

The data

The prior

The data

The posterior

## So the moral of the story…

- Bayesian thinking sounds very sensible
- We don’t do trials (experiments) in complete ignorance of what else is going on
- If we have *genuine* reasons to believe what the outcome might be, and we are prepared to state these *honestly* (and dispassionately)
- Then we ought to believe the posterior distribution

# Everyone's own beliefs…

- Why should *you* accept *my* prior belief?
- Why should *I* accept *your* prior belief?

- Prior beliefs are personal, hence, posterior beliefs are also personal

**Karl Popper**
**‘The Logic of Scientific Discovery’. Chapter I, Section 8. London, Hutchinson, 1959.**

“No matter how intense a feeling of conviction may be, it can never justify a statement. Thus I may be utterly convinced of the truth of a statement; certain of the evidence of my perceptions; overwhelmed by the intensity of my experience: every doubt may seem to be absurd. But does this afford the slightest reason for science to accept my statement? Can any statement be justified by the fact that Karl R Popper is utterly convinced of its truth? The answer is, ‘No’; and any other answer would be incompatible with the idea of scientific objectivity.”

# And my view…?