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**ICORD, Rome 2009.  
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** **S**  
**ayesian** **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...”

[ 412 ]

rule, is  $\frac{1}{n+1} \times E$  into the difference between

$$\frac{X^{\overline{p+1}} - q X^{\overline{p+2}}}{\overline{p+1} \quad \overline{p+2}} \quad \text{and} \quad \frac{x^{\overline{p+1}} - q x^{\overline{p+2}}}{\overline{p+1} \quad \overline{p+2}} = 12 \times 11$$

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

&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 guesses?

Here X and x being the same, we have n = 22, p = 20, q = 2, E = 231, and the required chance

$$\text{equal to } \frac{1}{n+1} \times E \times \frac{X^{\overline{p+1}} - q X^{\overline{p+2}} + q \times \frac{q-1}{2} \times X^{\overline{p+3}}}{\overline{p+1} \quad \overline{p+2} \quad \overline{p+3}}$$

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

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

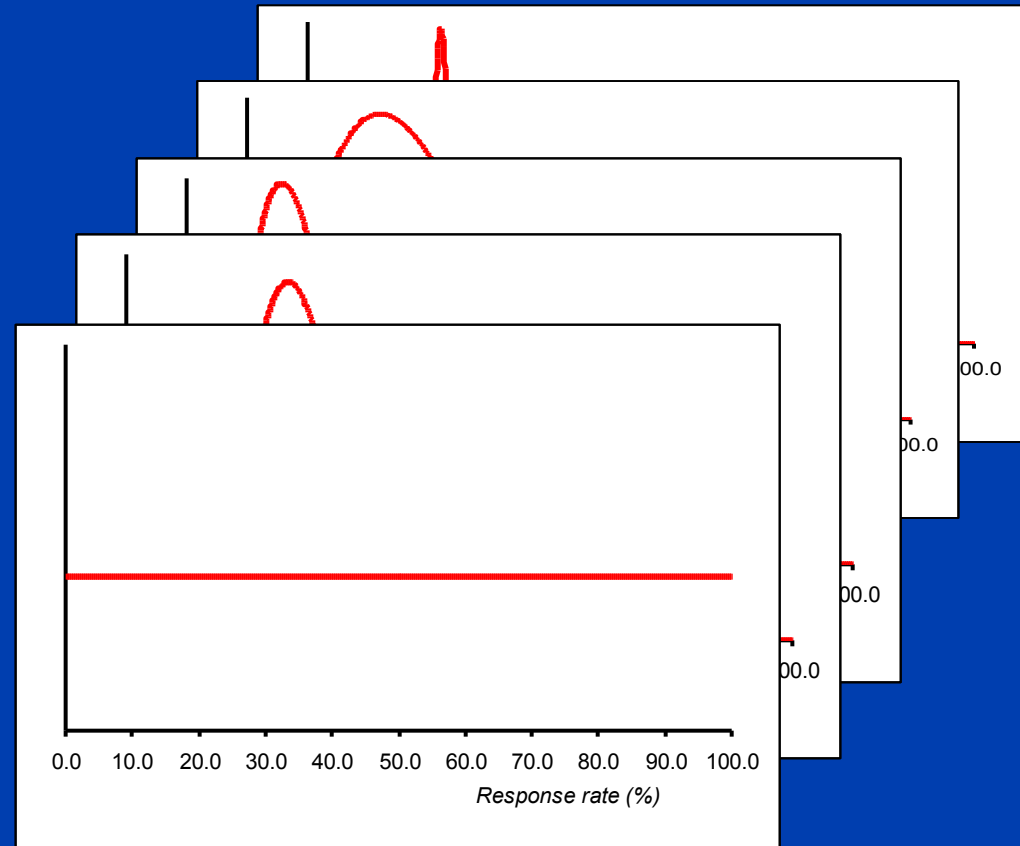
### A single arm trial for a promising new anti-cancer compound

- 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%

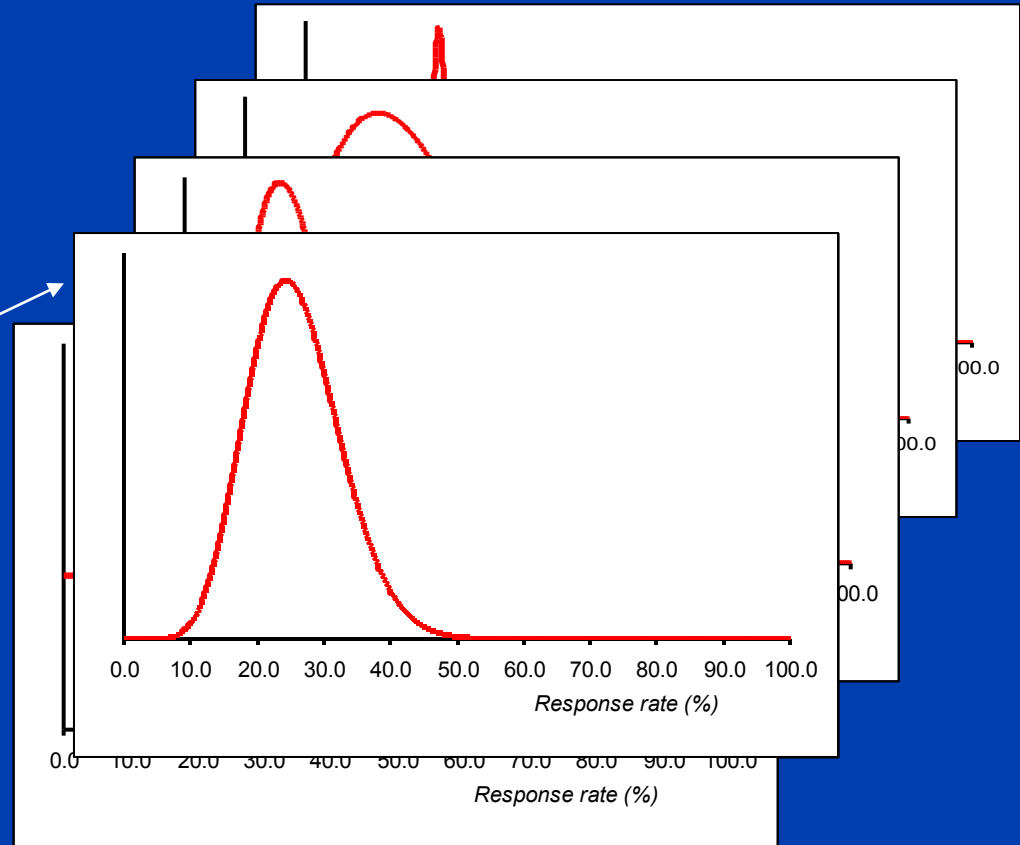
- And I'm really convinced
- Or I'm a fairly unsure
- I'm a sceptic (15%)
- I'm an optimist (25%)
- Actually, I haven't really got a clue



# Set out what we already know

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

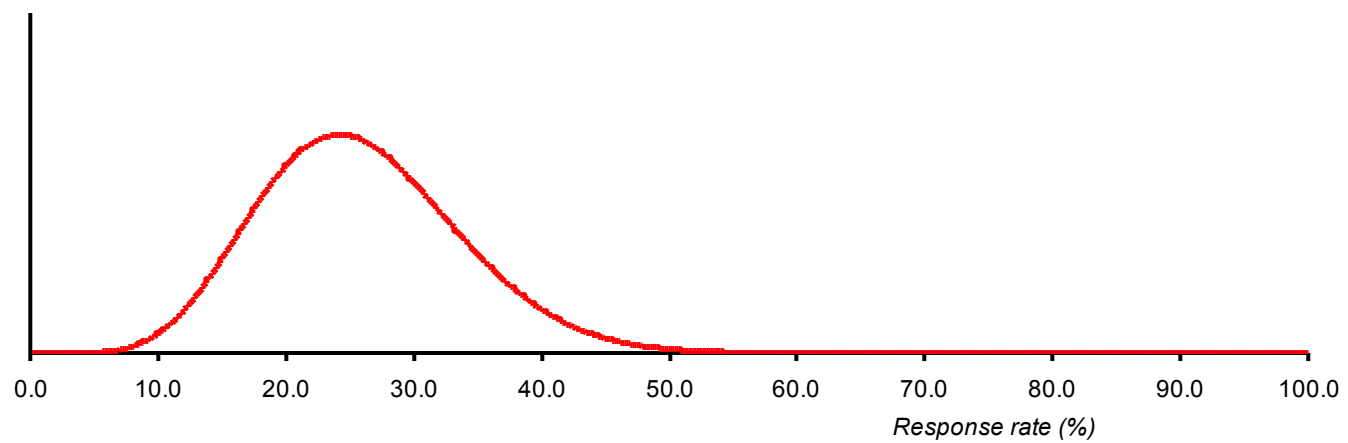
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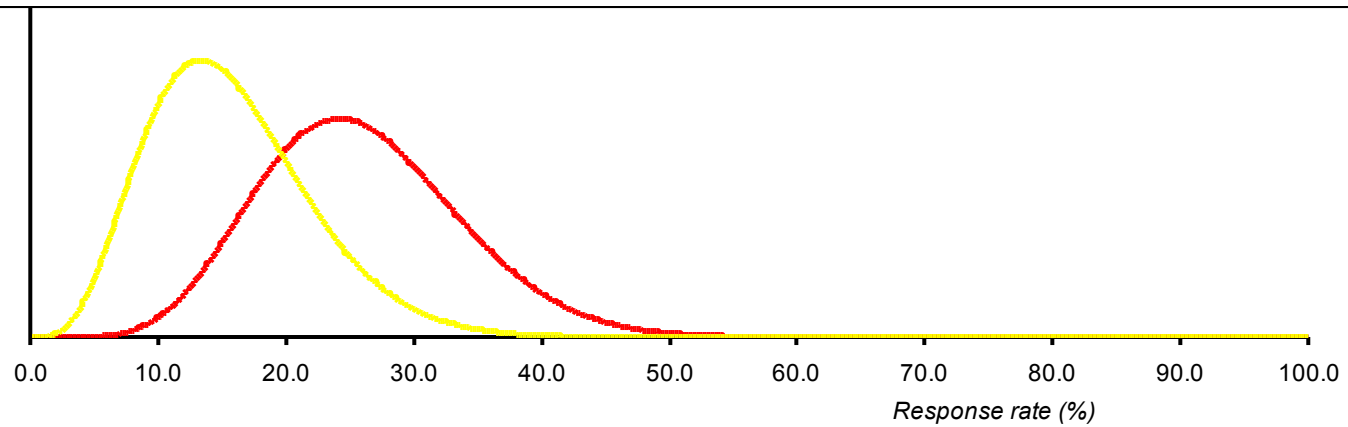
## Decide on sample size

This may be exactly the same “classical” trial

- ~~We recruit and treat 30 patients~~  
(let's assume  $n=30$ )
- 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...

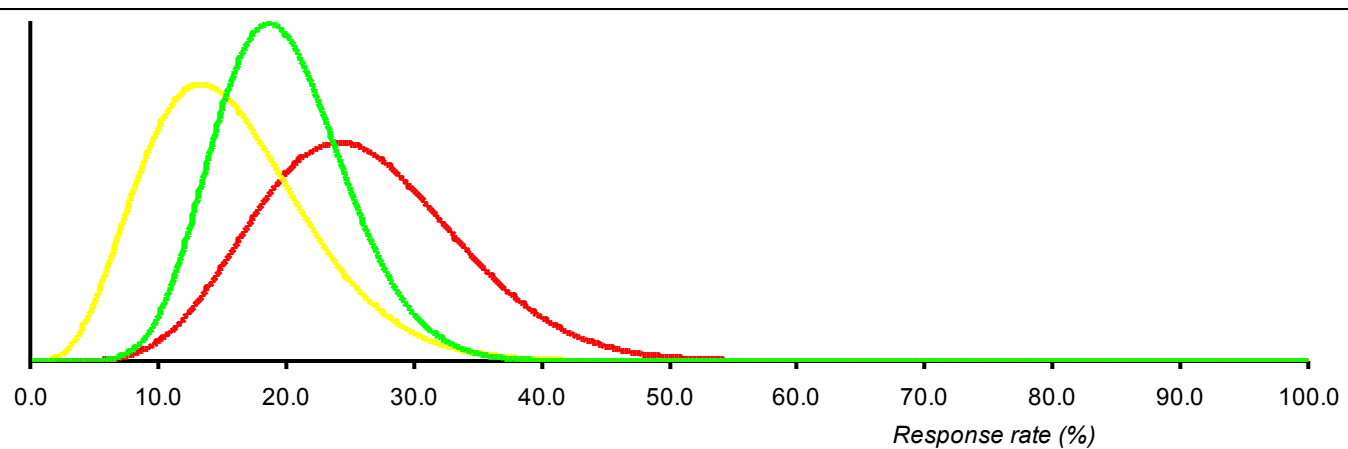


The prior



The prior

The data

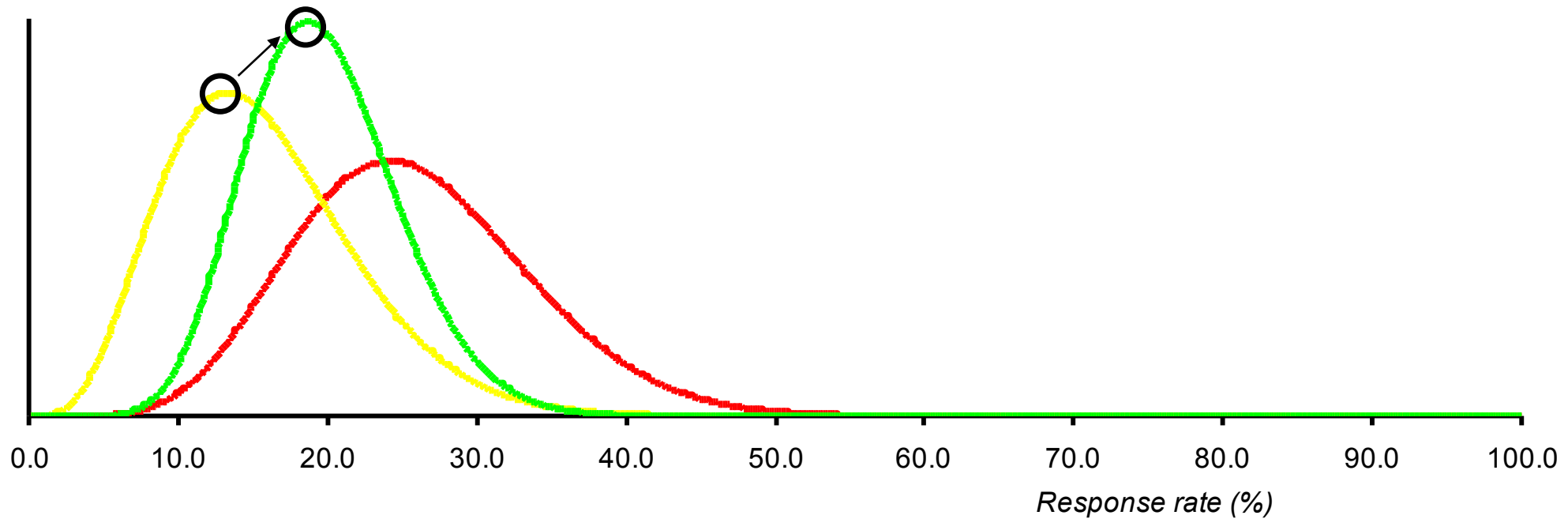


The prior

The data

The posterior

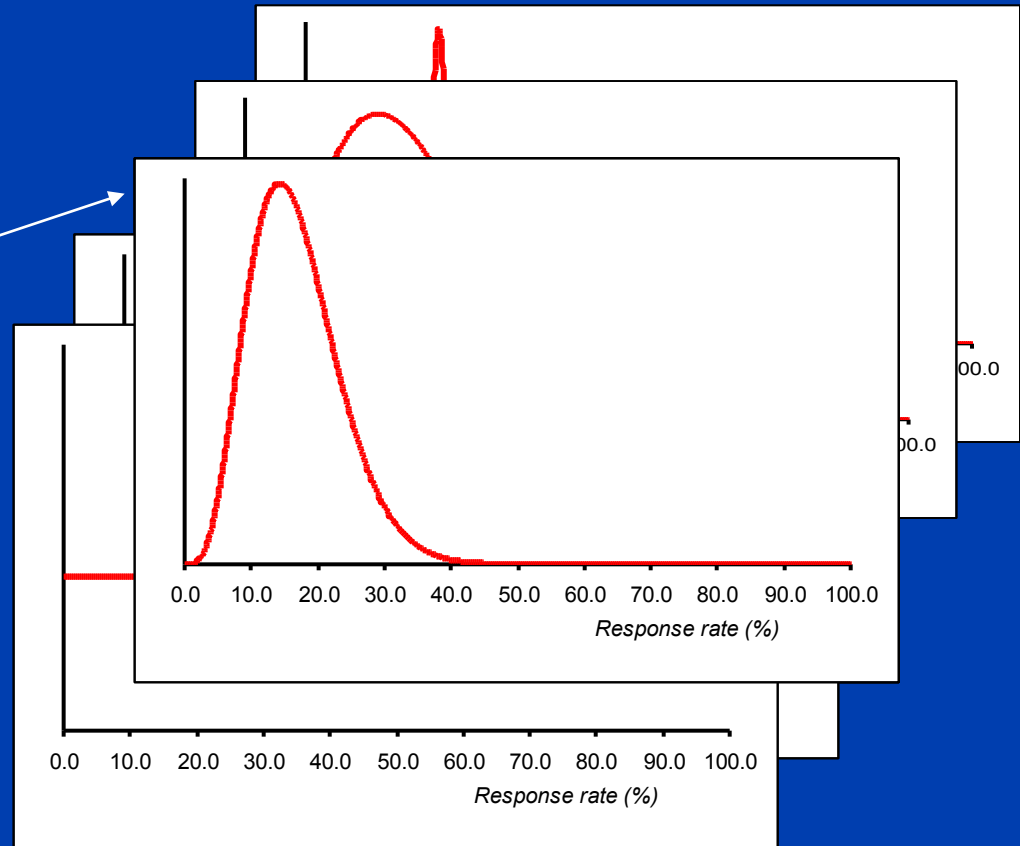
The prior (at 25%) has “rescued” a trial that showed poor results (13%)





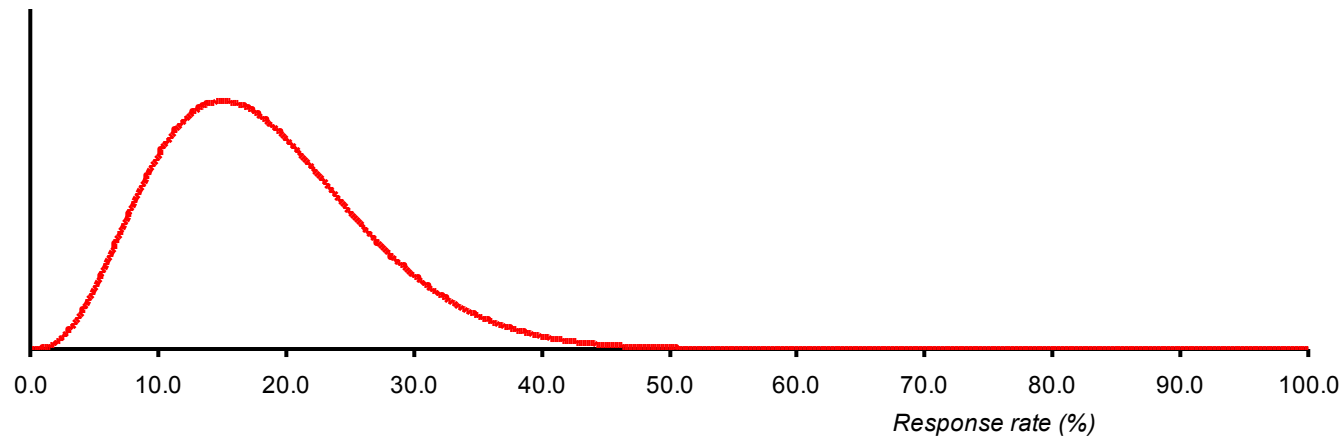
# But let's look at another example...

- 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

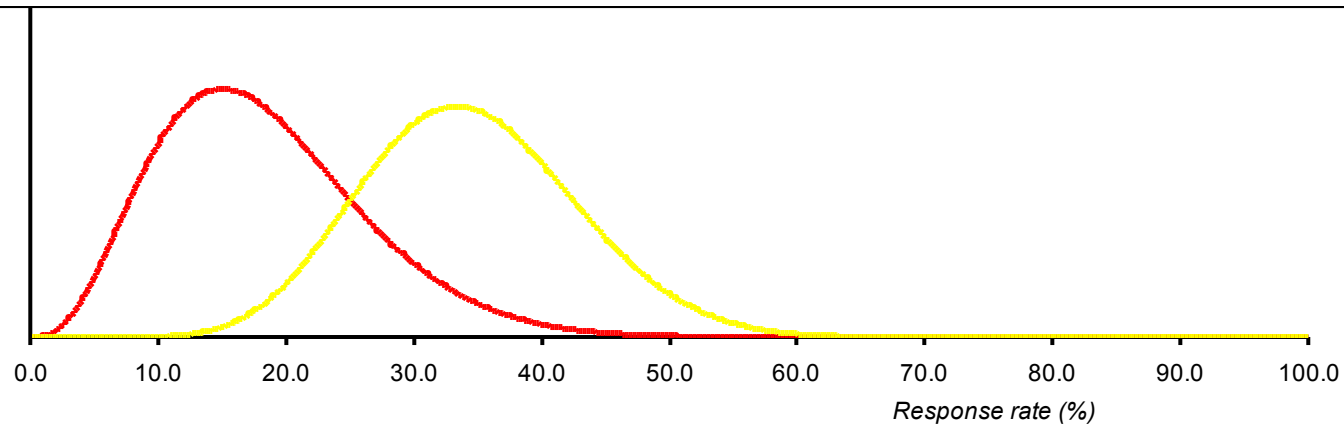


## We do the same experiment

- 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...

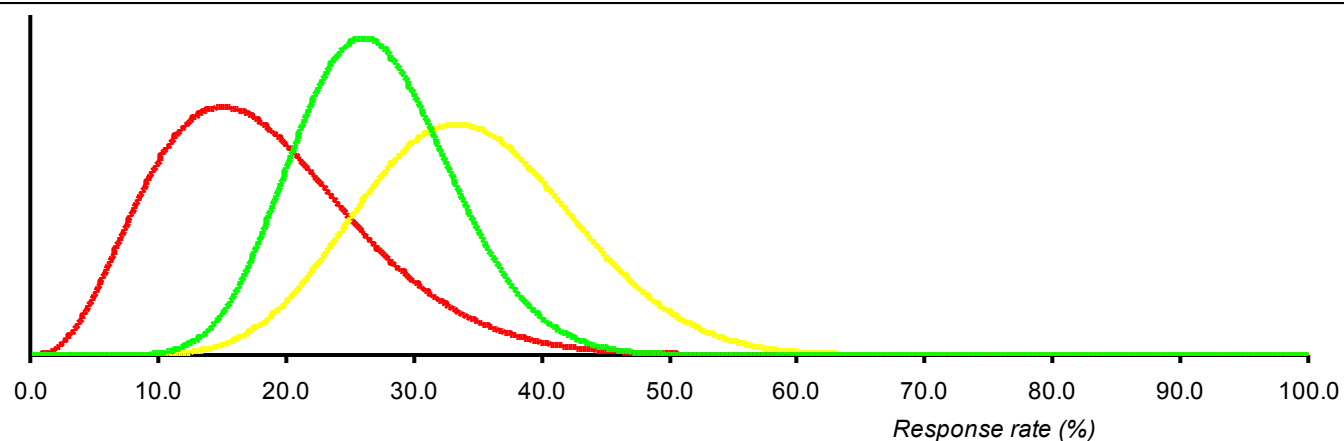


The prior



The prior

The data

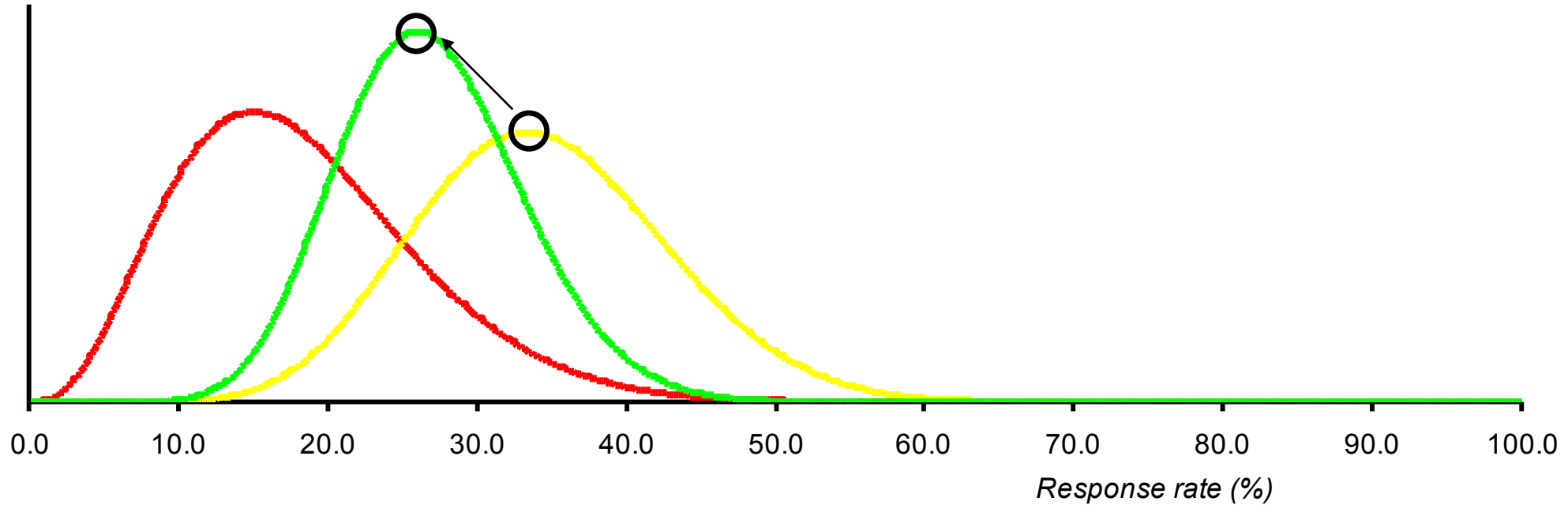


The prior

The data

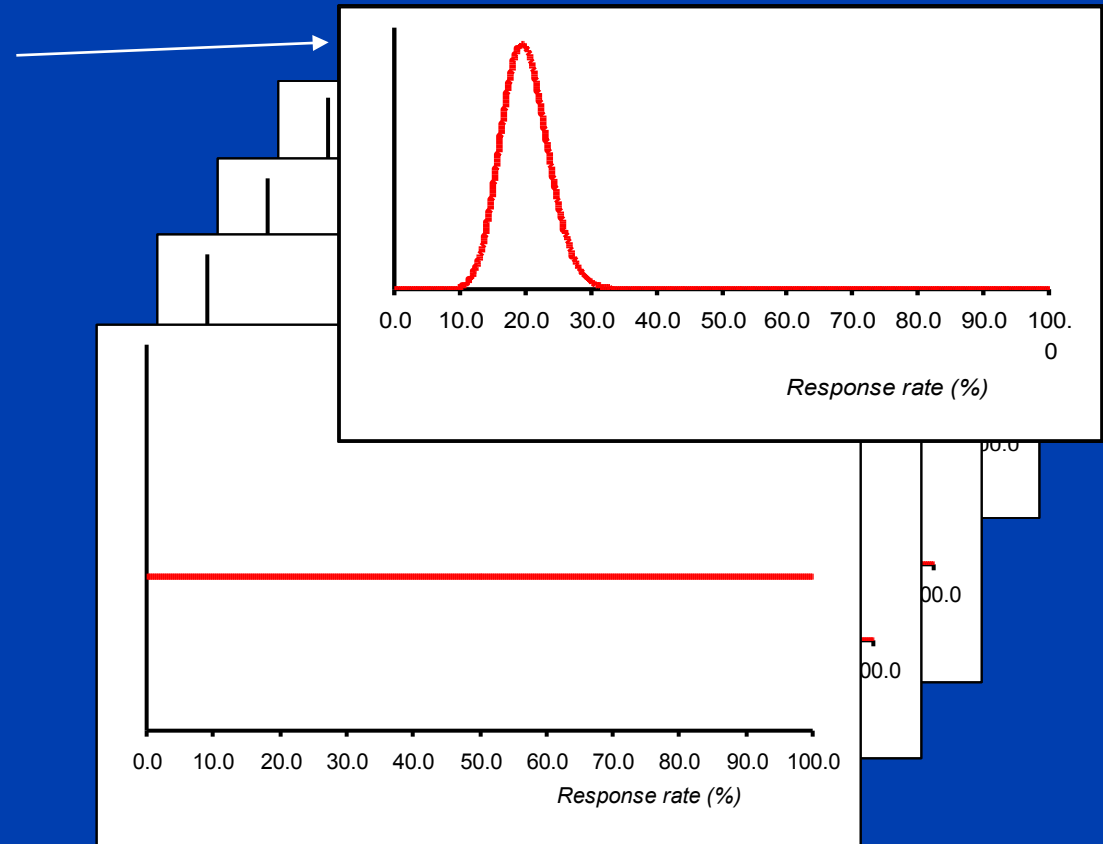
The posterior

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



# Worst of all, we can abuse the system...

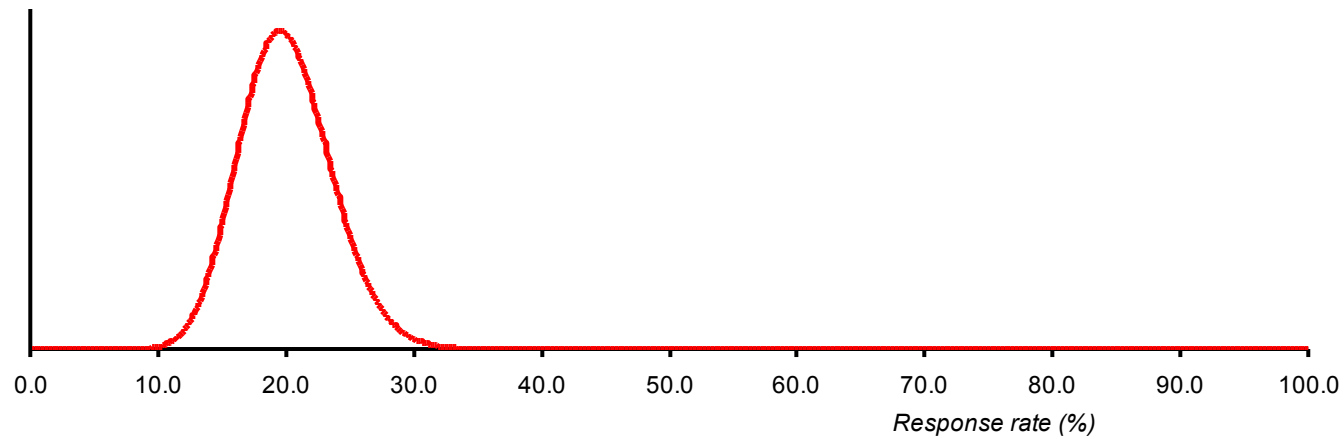
- And I'm <sup>reasonably</sup> ~~really~~ convinced
- Or I'm a fairly unsure
- I'm a sceptic (15%)
- I'm an optimist (25%)
- Actually, I haven't really got a clue



## We do a tiny “experiment”

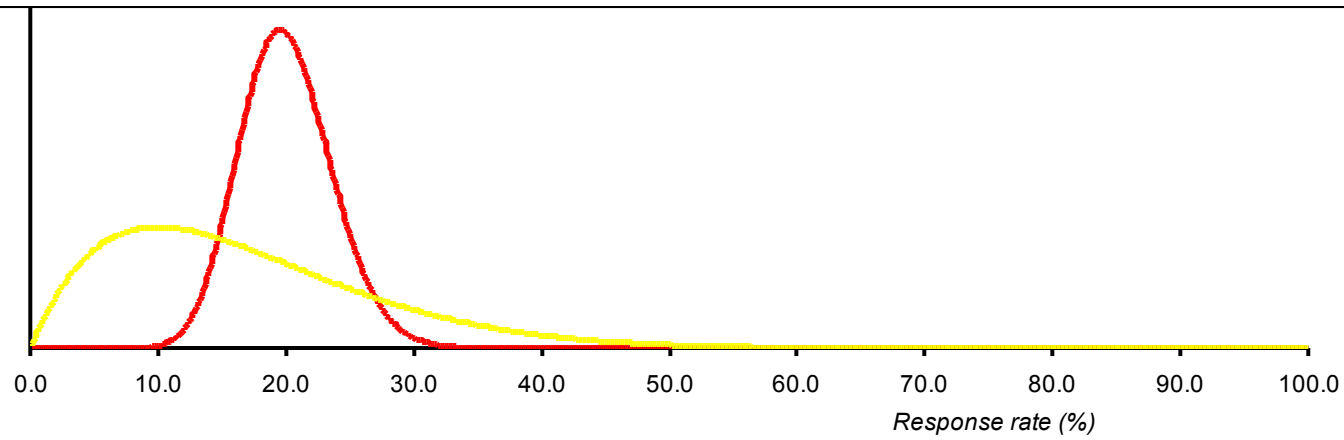
- We recruit and treat 10 patients
- We see 1 of them “respond”
- So I used to believe 20% was what I’d expect; now I have data suggesting it’s only 10%
- I combine these two (20% and 10%) together...

The prior



The prior

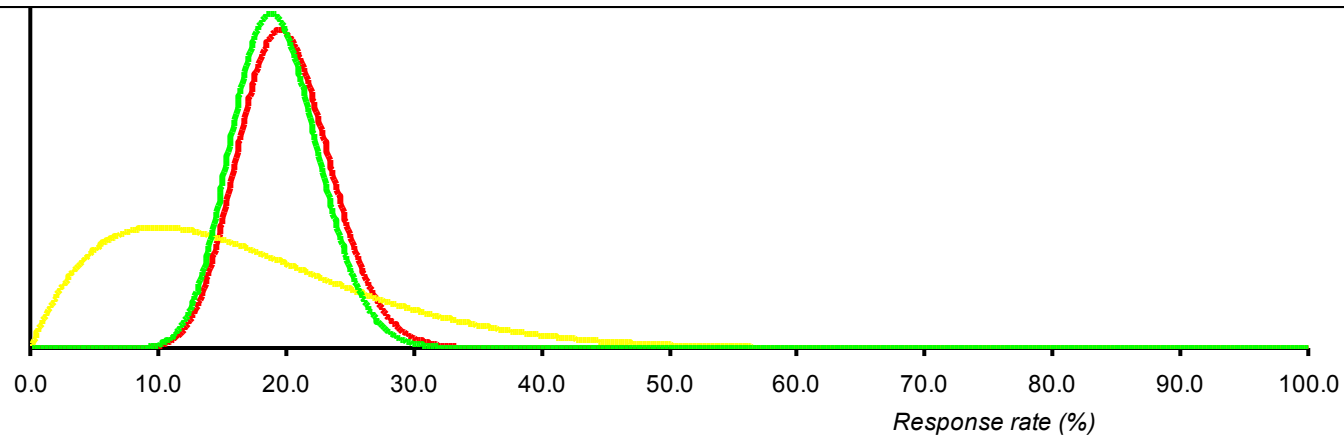
The data



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...?

