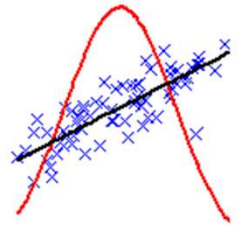

Vaccine trials in the age of COVID-19: issues and inferences

Stephen Senn

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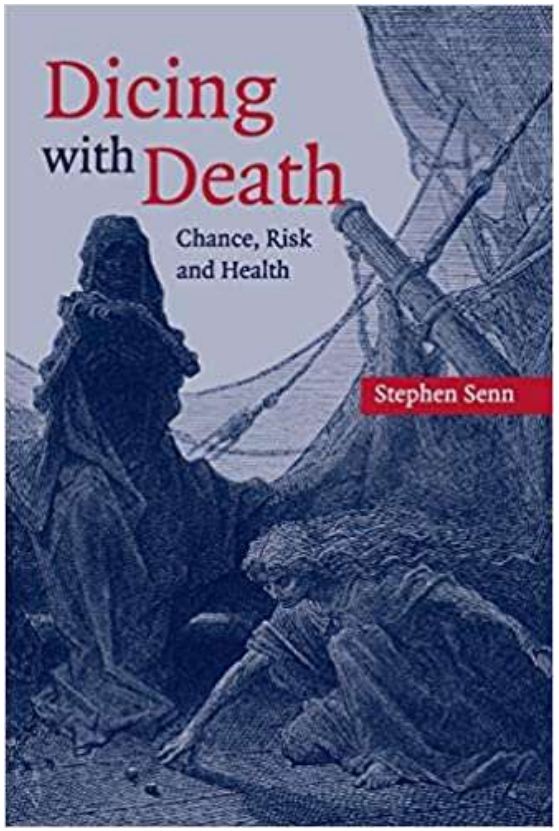
@stephensenn

http://www.senns.uk/Blogs.html

Talk outline

- Background
  - Infectious processes
  - Reporting data
  - Herd immunity?
  - COVID Mortality
- Five vaccine trials
  - General overview
- The AZ/Oxford study
- The Pfizer study
- Some general design issues
- Conclusions?



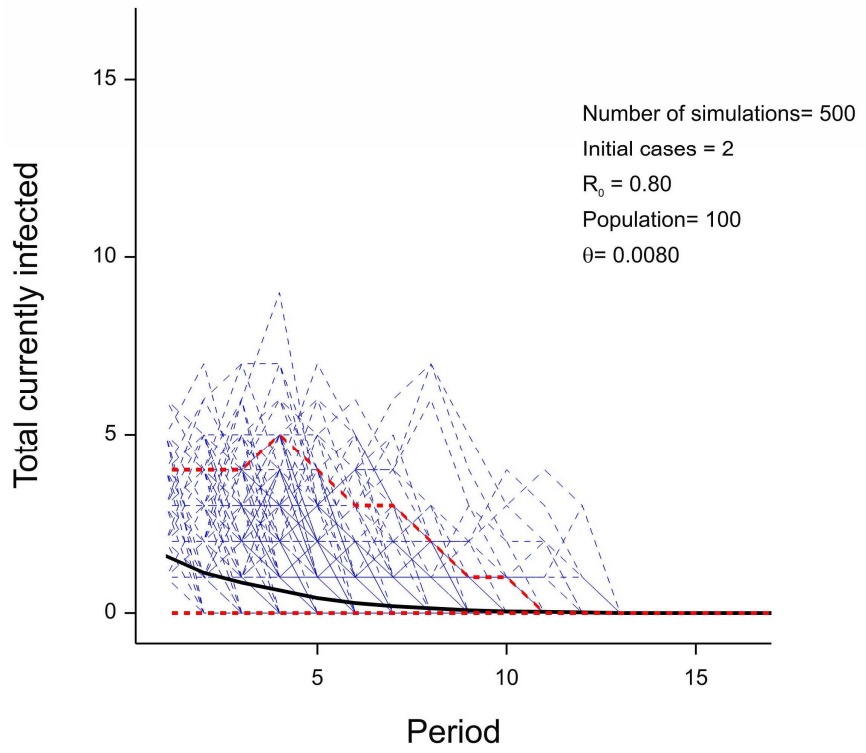
This is being prepared for a 2nd edition with an extra COVID chapter. The material for this talk comes from that.

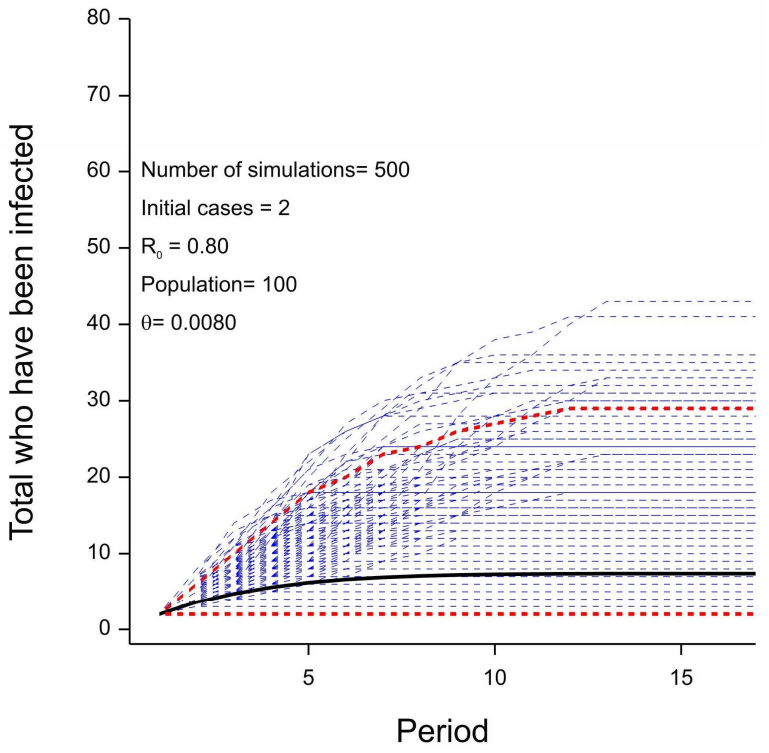
Background

What’s happening and why vaccines matter

Simulated toy epidemic
$R_0 < 1$

Thick black line is median
Thick dashed red lines are 2.5% and 97.5% quantiles





Simulated toy epidemic
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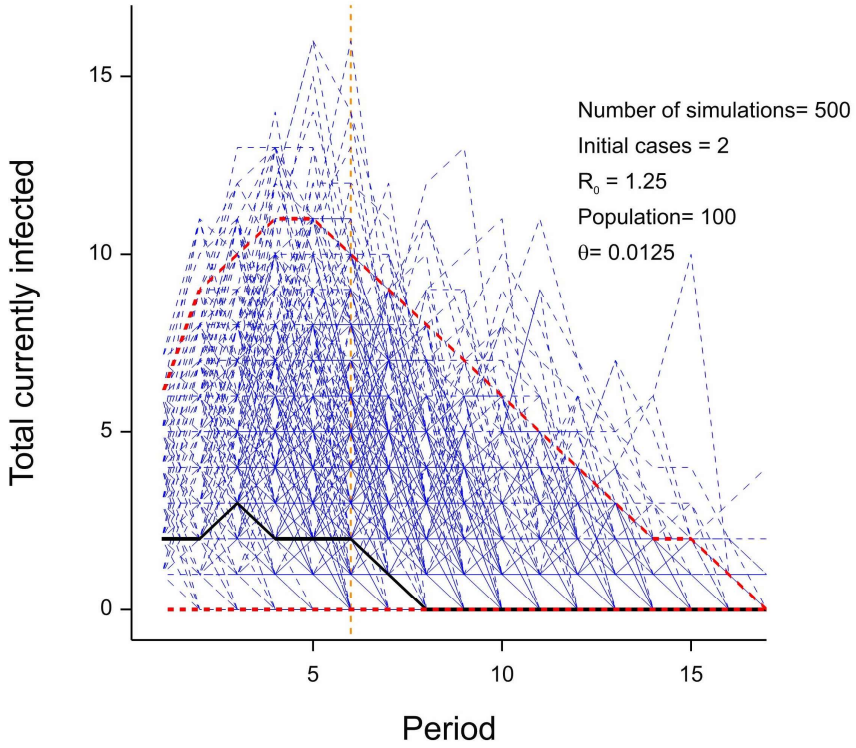
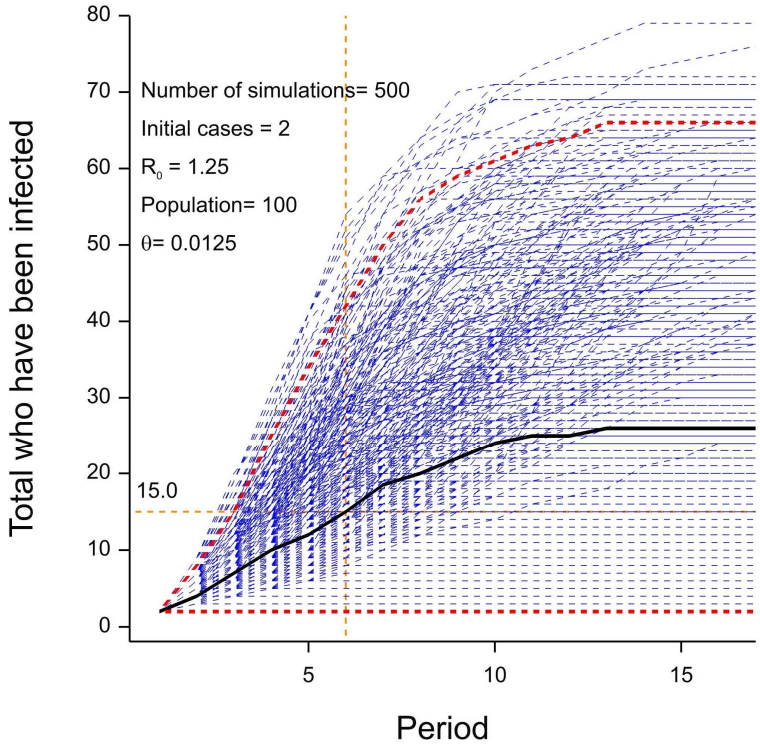
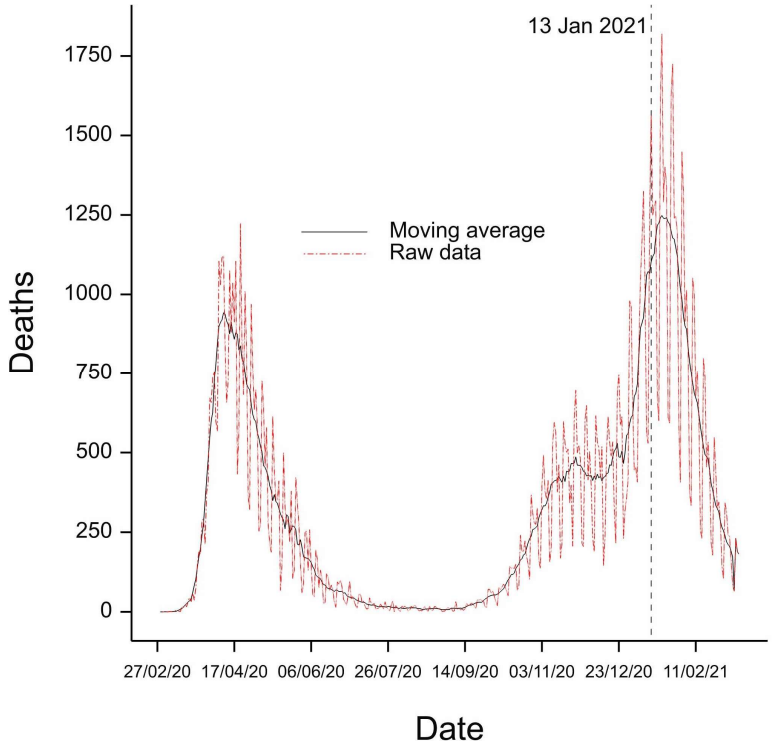
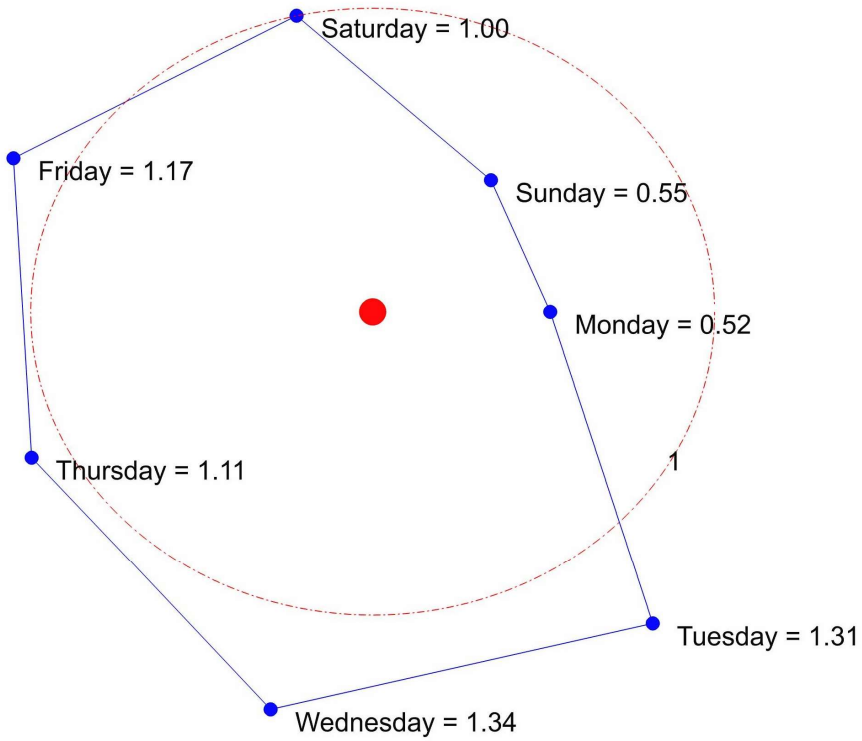




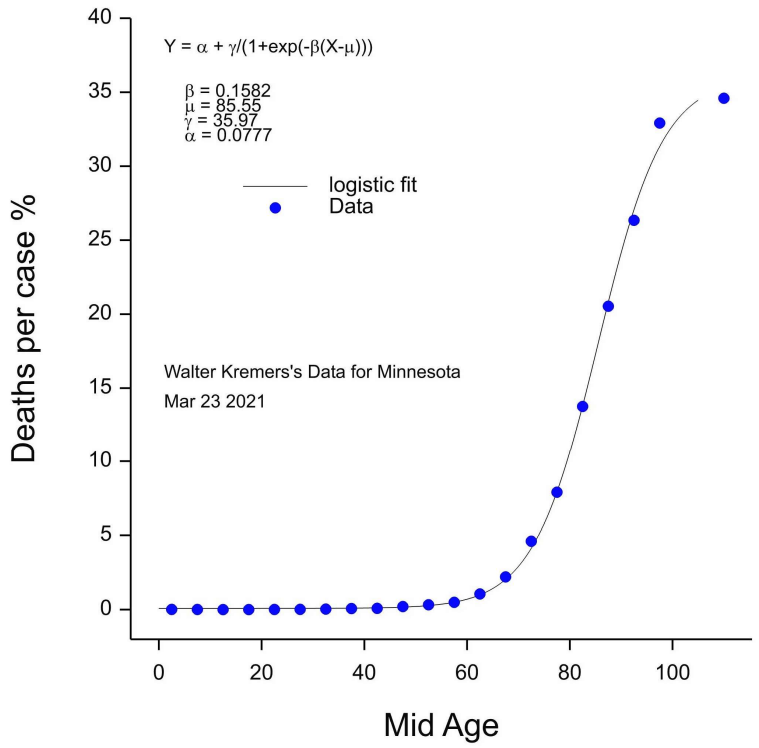
Pay attention to reporting issues

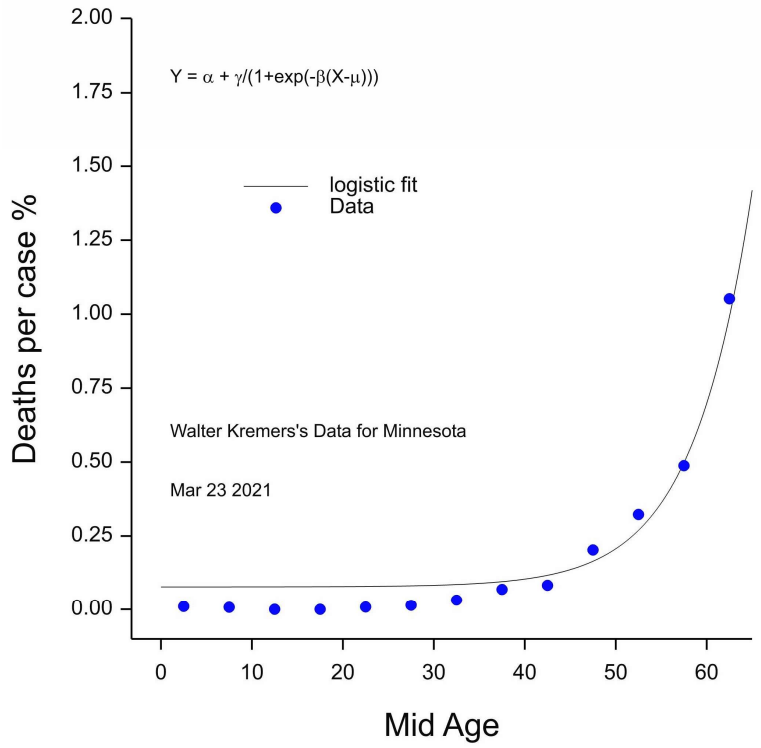
Daily deaths UK



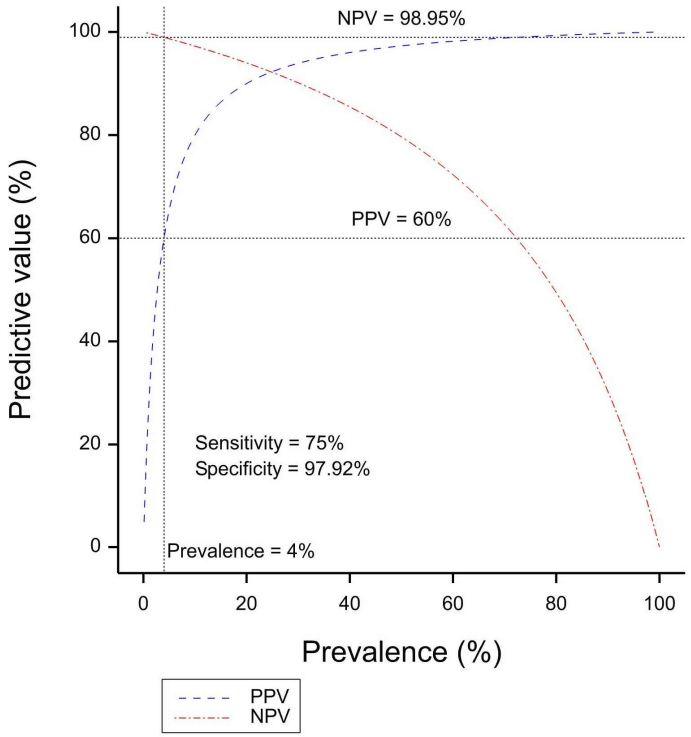


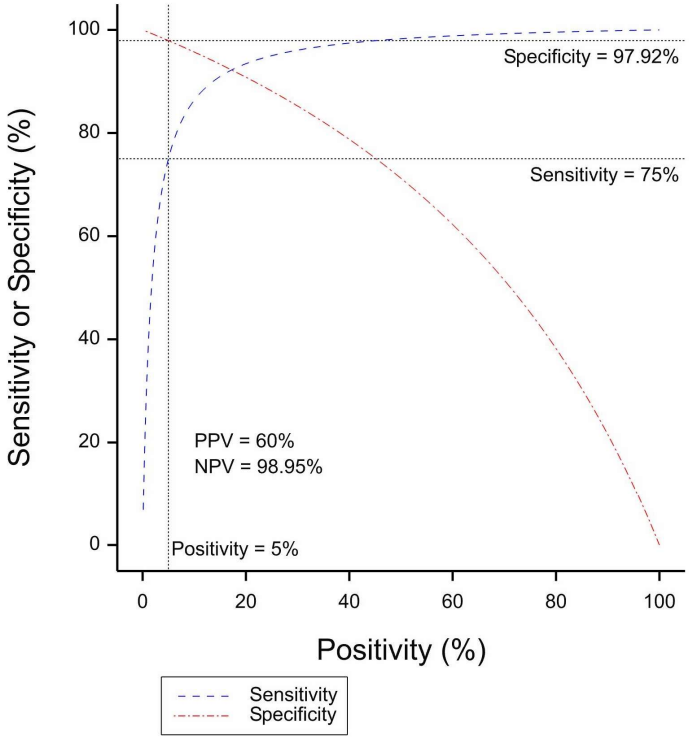
Deaths in Minnesota
(Data kindly provided by Walter Kremers)





How do you like your Bayes?

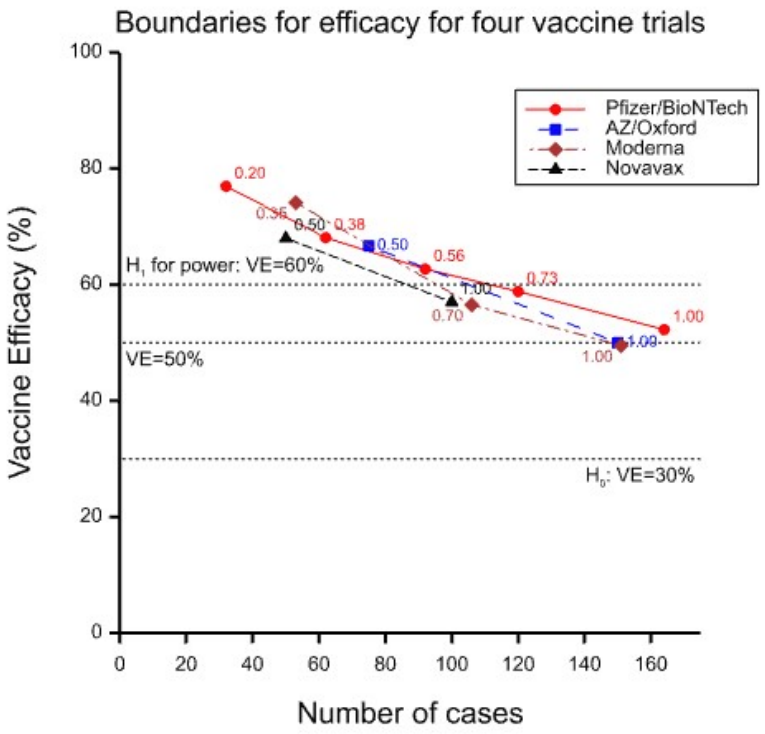




Five vaccine programmes

Similarities and differences

Design of five large trials



Sponsor or organiser	Shots	Number treatment	Number control	Events targeted	Assumed control rate %	H_0 efficacy %	H_1 efficacy %	Looks
Pfizer/ BioNTech	2	21,999	21,999	164	0.65	30	60	5
AZ/ Oxford	2	20,000	10,000	150	0.80	30	60	2
Moderna	2	15,000	15,000	151	0.75	30	60	3
Novavax	2	7,500	7,500	100		30	60	2
J & J Janssen	2	20000	20000	154	?	30	60	Continuous

Control rates are per 6 month. (Novavax rate not given in protocol J & J has a rather complicated story.)

A surprisingly effective simple analysis

- Condition on the total cases
- Use

Vaccine infection rate

Placebo infection rate

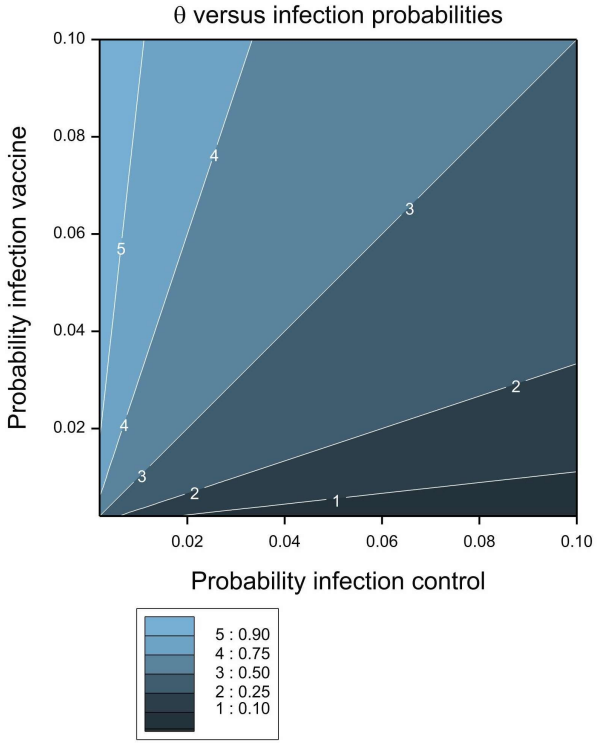
$$\theta = \frac{\pi_v}{\pi_v + \pi_p},$$

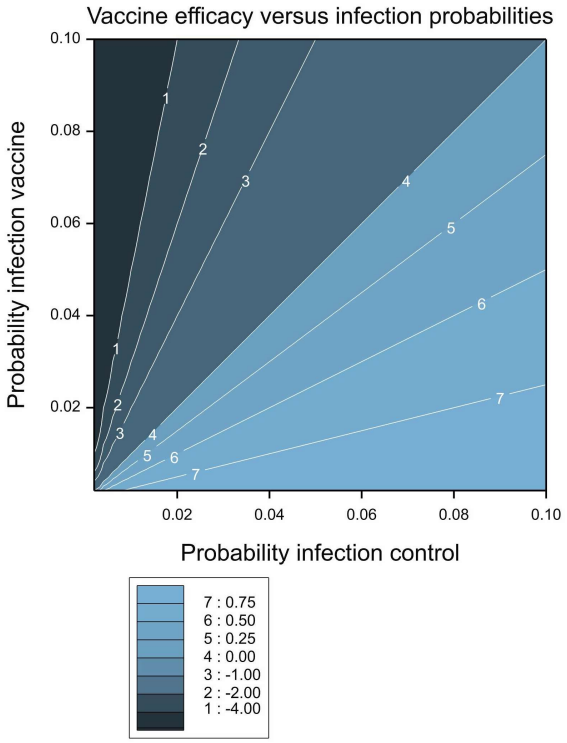
$$\hat{\theta} = \frac{Y_v/n_v}{Y_v/n_v + Y_p/n_p} \approx \frac{Y_v}{Y_v + Y_p}, if\ n_p \approx n_v \quad Y_v \sim Bin\left(\theta, Y_v + Y_p\right)$$

- Calculate exact binomial confidence limits
- Transform to vaccine efficacy scale

$$VE = \frac{\pi_p - \pi_v}{\pi_p} \rightarrow VE = \frac{2\theta - 1}{\theta - 1}$$

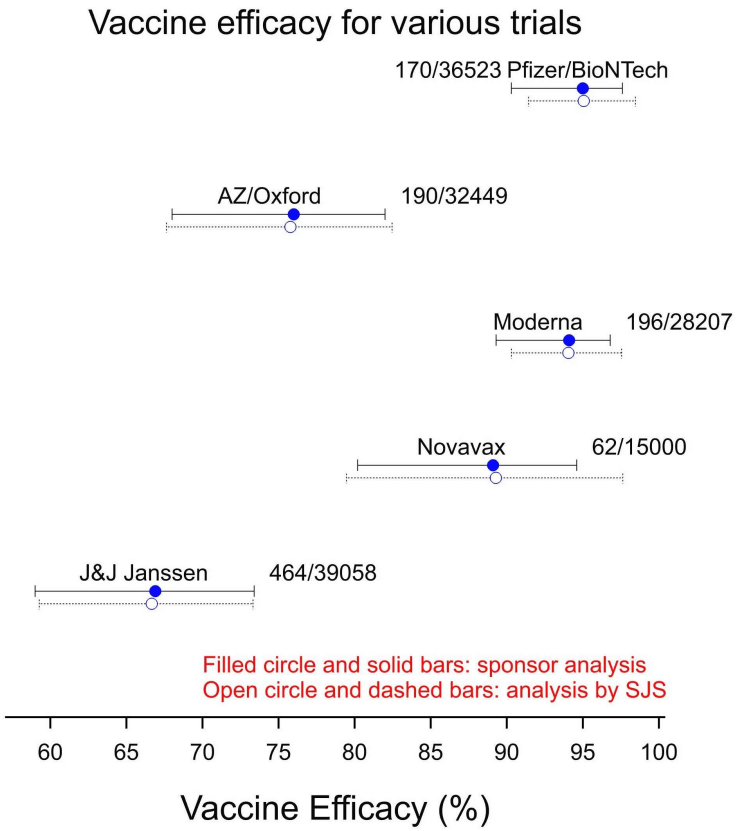
Contours of efficacy





Results of five large vaccine trials

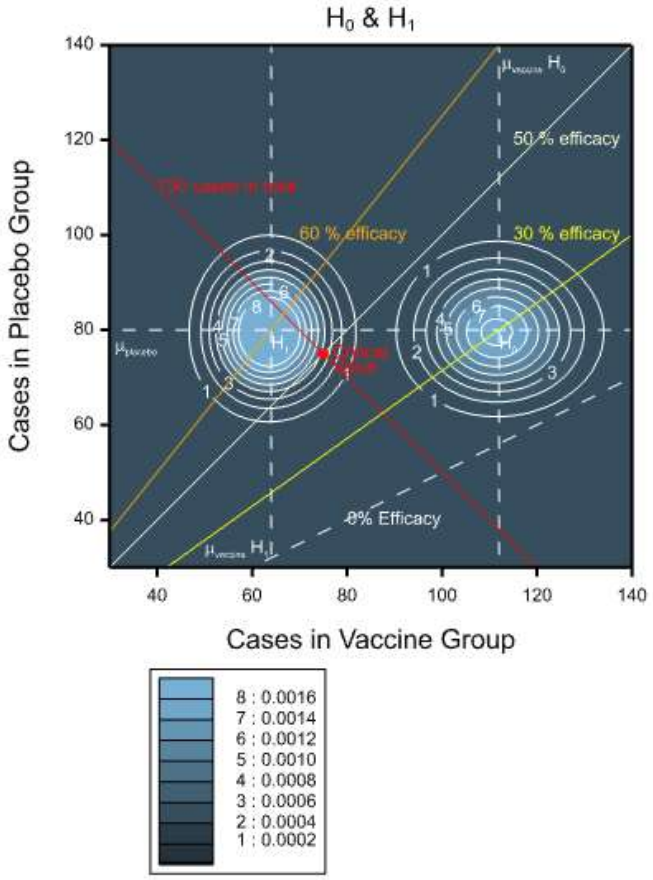
Sponsor	Vaccine Subjects	Control Subjects	Vaccine Cases	Control Cases
Pfizer/ BioNTech	18198	18325	8	162
AZ/ Oxford	21632	10817	62	128
Moderna	14134	14073	11	185
Novavax	7500	7500	6	56
J & J Janssen	19514	19544	116	348



The AZ/Oxford programme

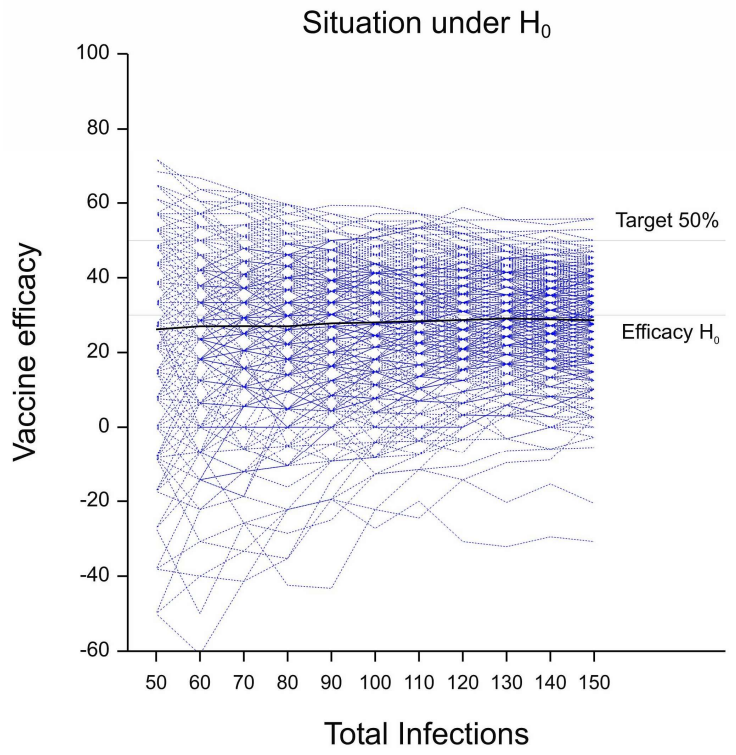
Various issues

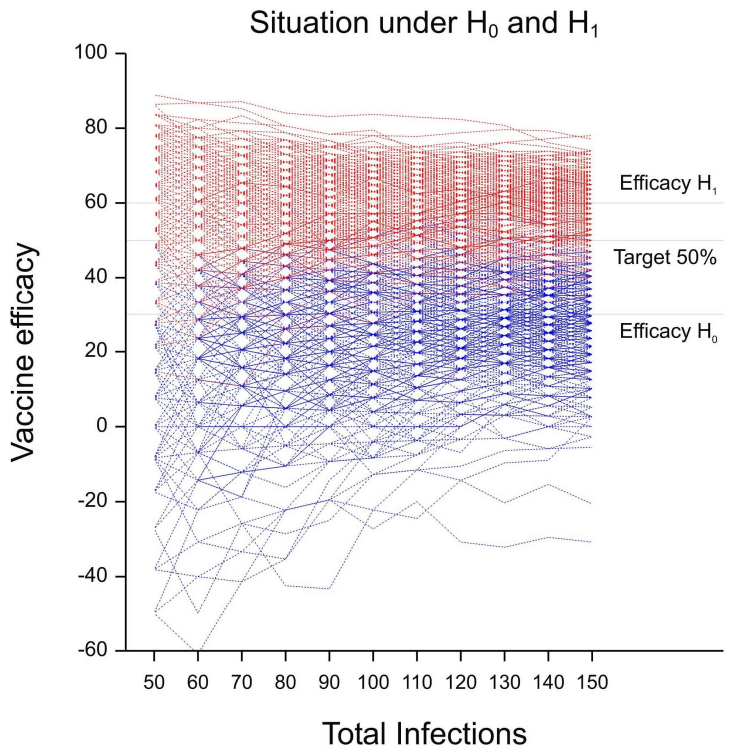
AZ/Oxford Phase III study



- H_0: vaccine efficacy 30%
- H_1: vaccine efficacy 60%
- 2:1 randomisation
- Great uncertainty as to how many cases in total will occur
- However, for analysis this is largely irrelevant
- It is the split of cases vaccine v placebo that matters

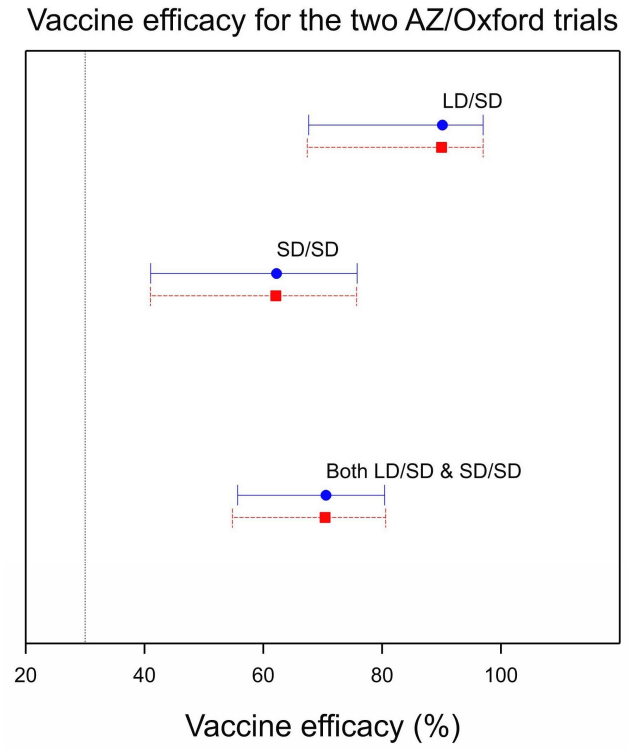
Some trial simulations



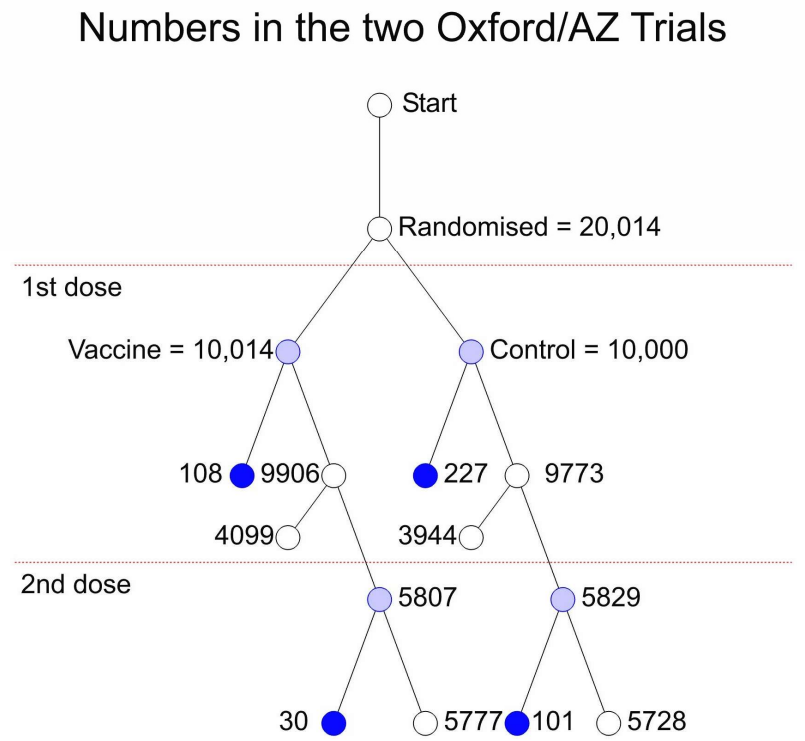


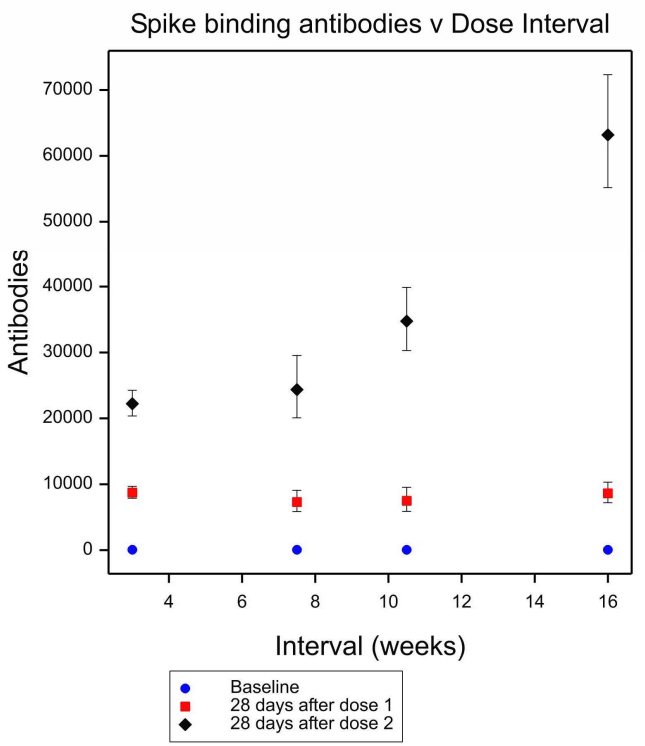
The AZ/Oxford Registration Story

- Registration was not sought using the single large planned study
- It was based on two incomplete smaller studies
- As a result of an error some subjects were given a lower dose
- A curious finding was that efficacy was apparently greater for the lower dose
- However the dosing interval was larger for the lower dose and this provides a plausible explanation

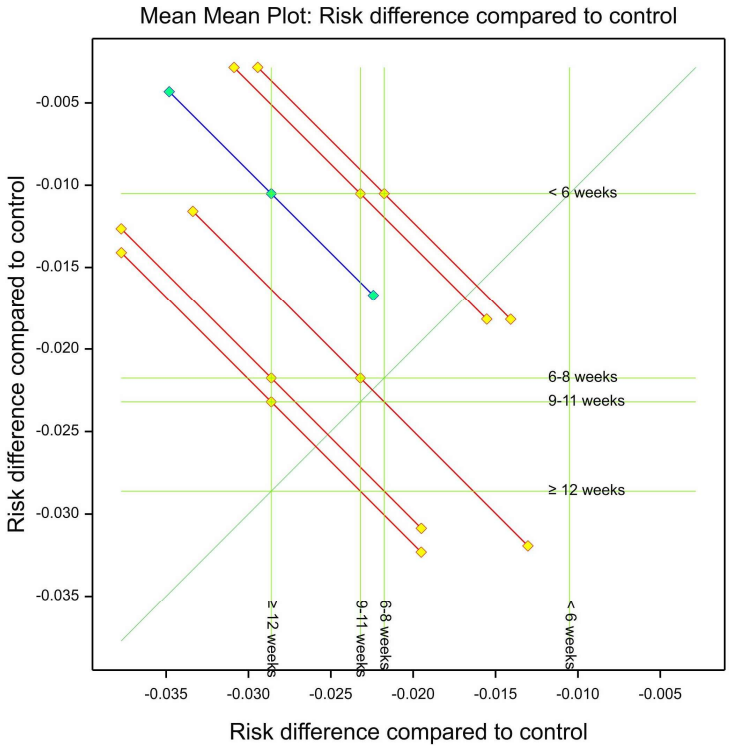


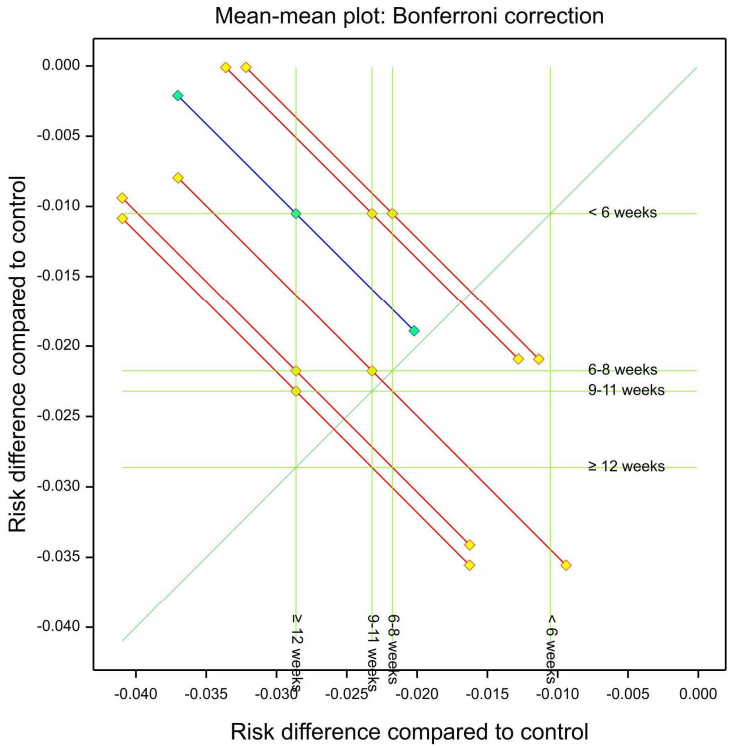
AZ/Oxford Registration Data





Comparison of results by interval



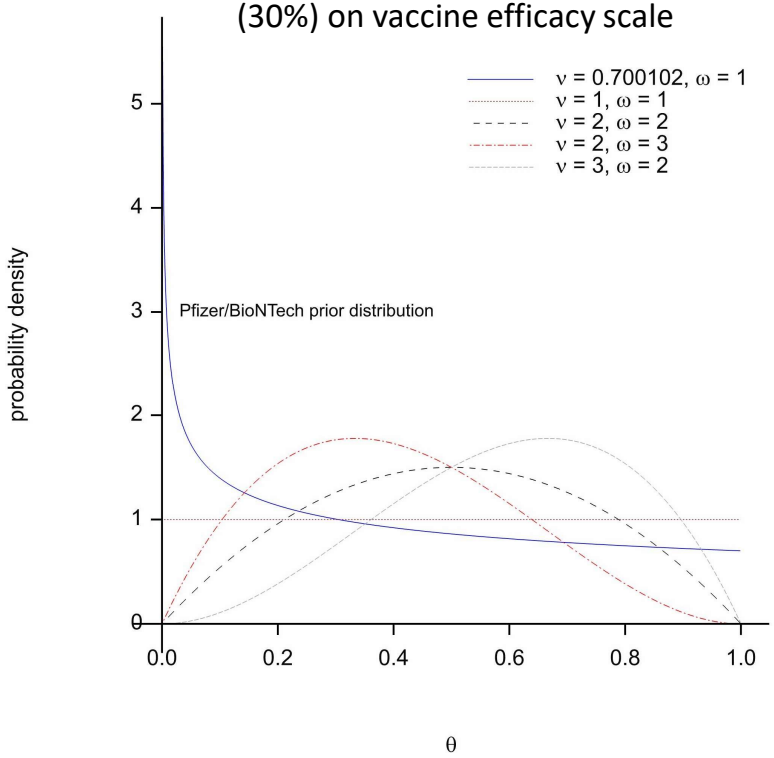


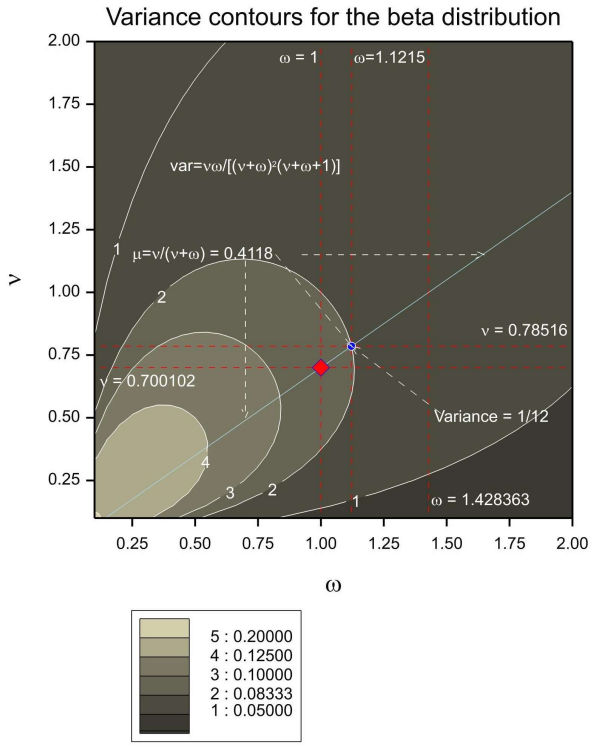
Pfizer/BioNTech

First to report

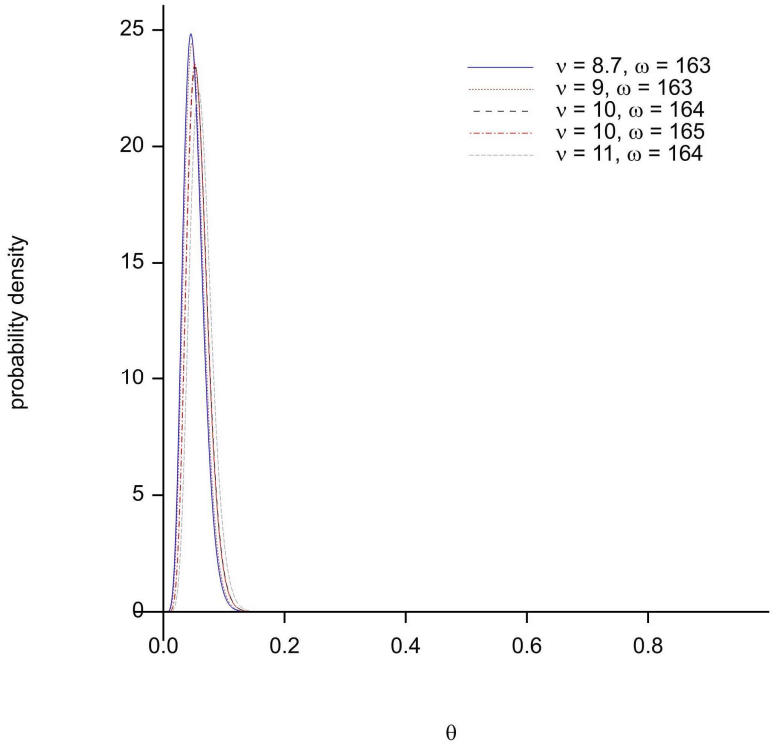
Pfizer's strange choice of prior distribution

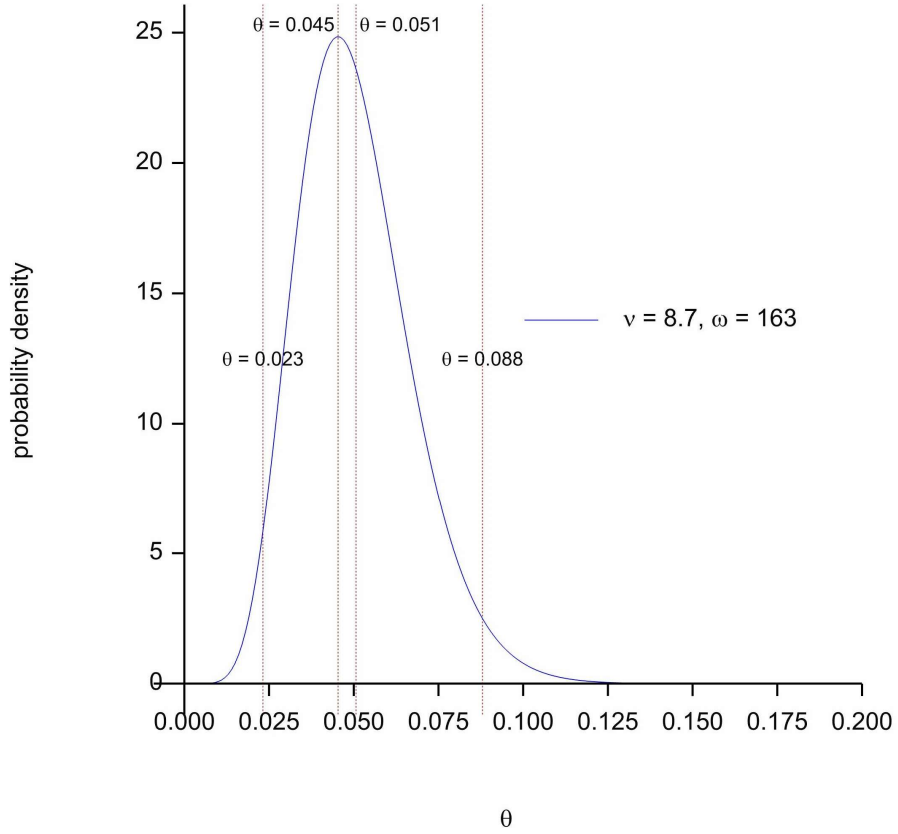
Gives mean 0.4118, which transforms to 0.3 (30%) on vaccine efficacy scale



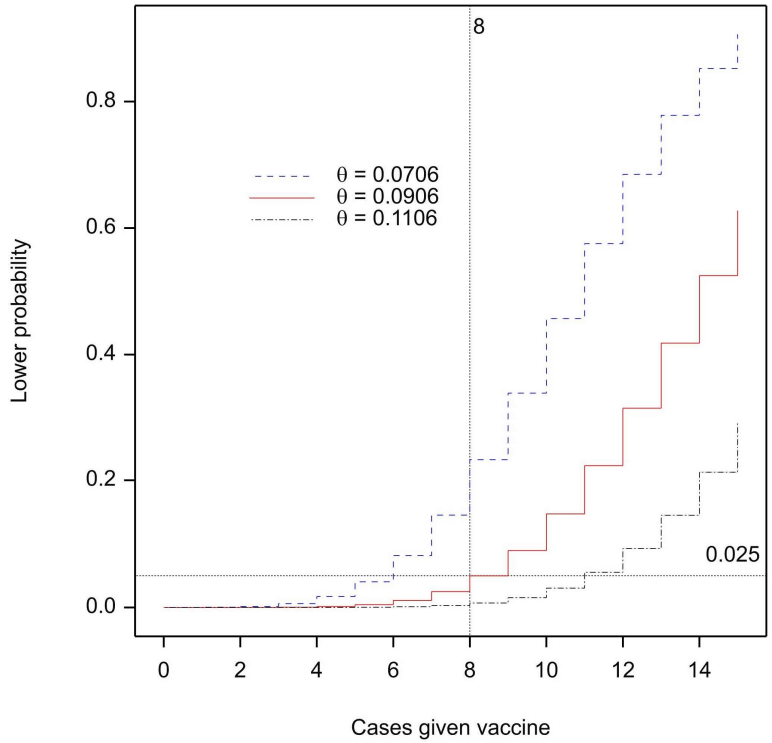


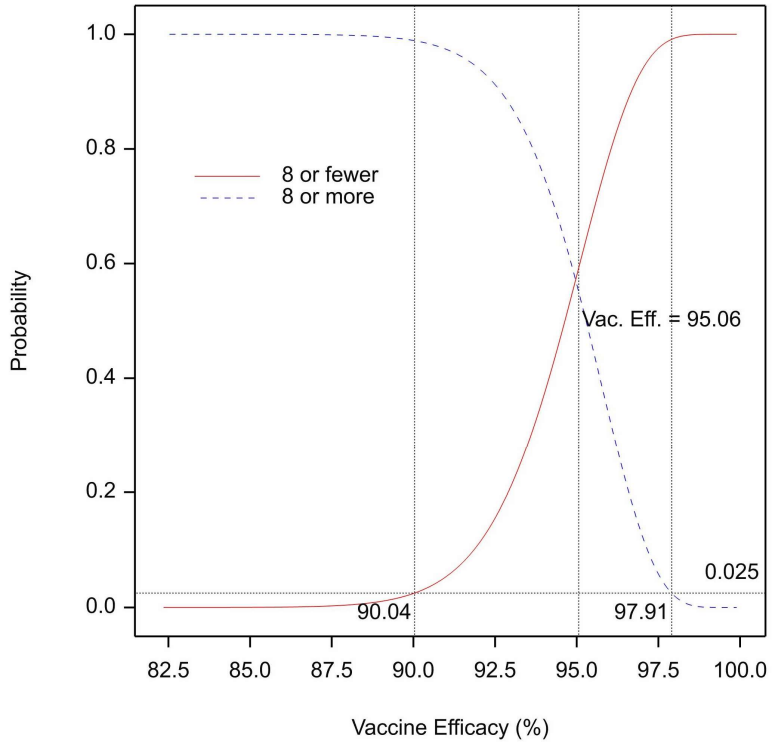
Posterior distributions





Pfizer/BioNTech
Confidence intervals





Confidence or credibility?

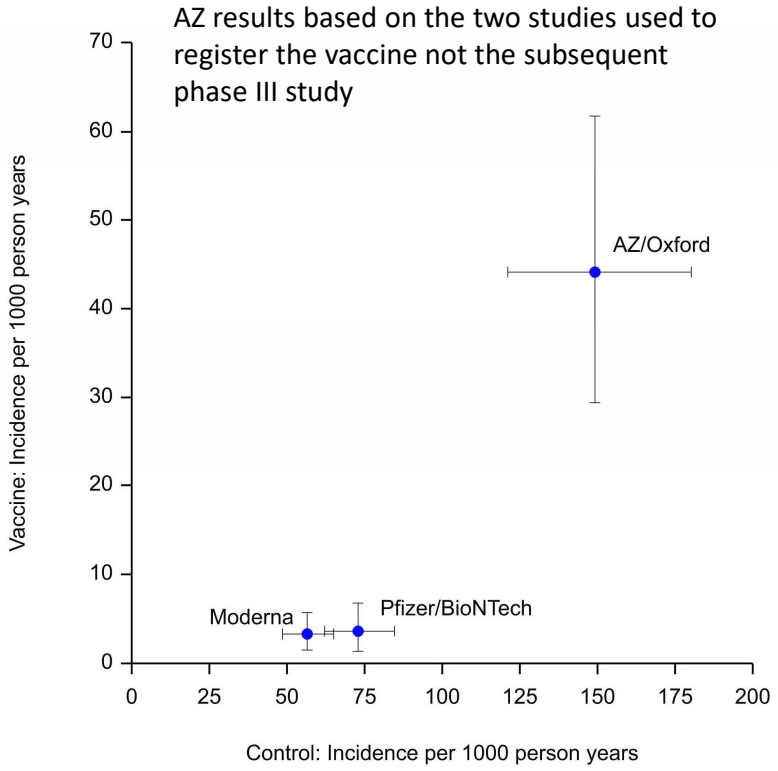
Type	Point estimate	Lower Limit	Upper Limit
Pfizer/BioNTech full model credible	95.0%	90.3%	97.6%
Simple credible (mean θ)	94.7%	90.4%	97.6%
Simple credible (mode θ)	95.2%		
Simple credible (median θ)	94.9%		
Simple confidence	95.0%	90.0%	97.9%

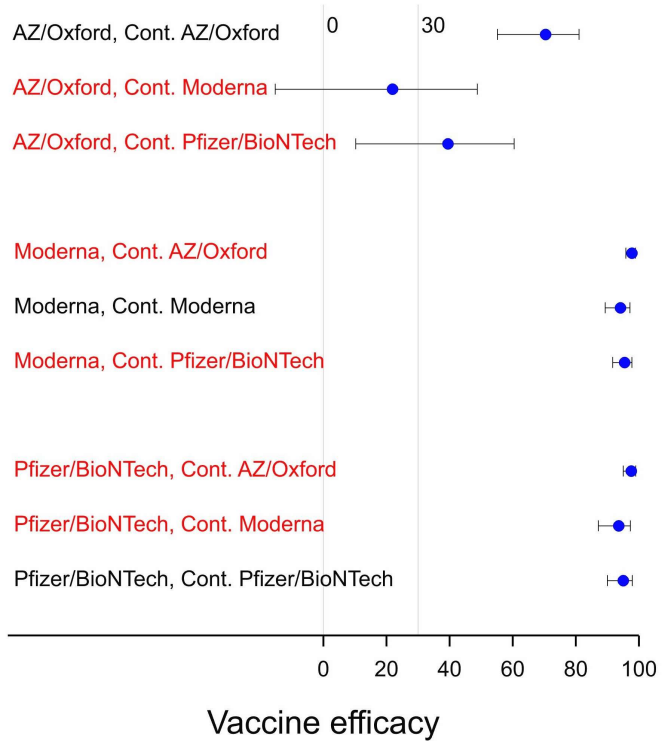
General Design Issues

And also analysis issues

And also practical matters

The value of concurrent control





The Value of Blinding

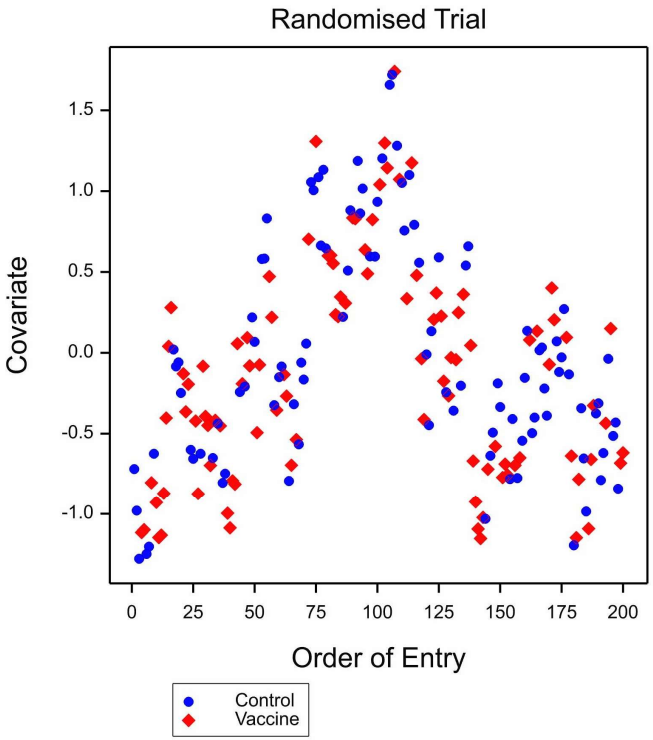
General Points

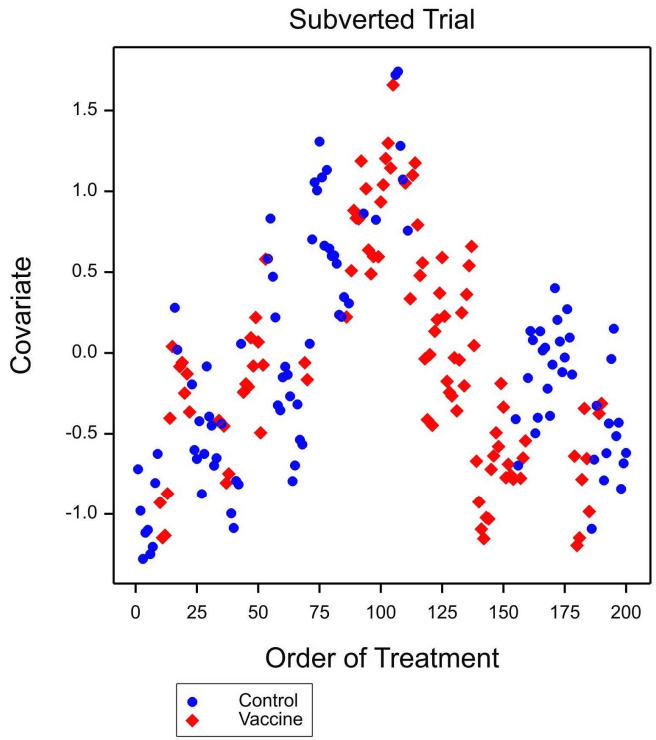
- If we run a trial double blind then we not only prevent subjective bias but we support the randomisation process
- If we run a parallel group trial we make it impossible for clustering to occur
- However even if we design a parallel group trial running it as open may lead to clustering

Difficulties with open trials

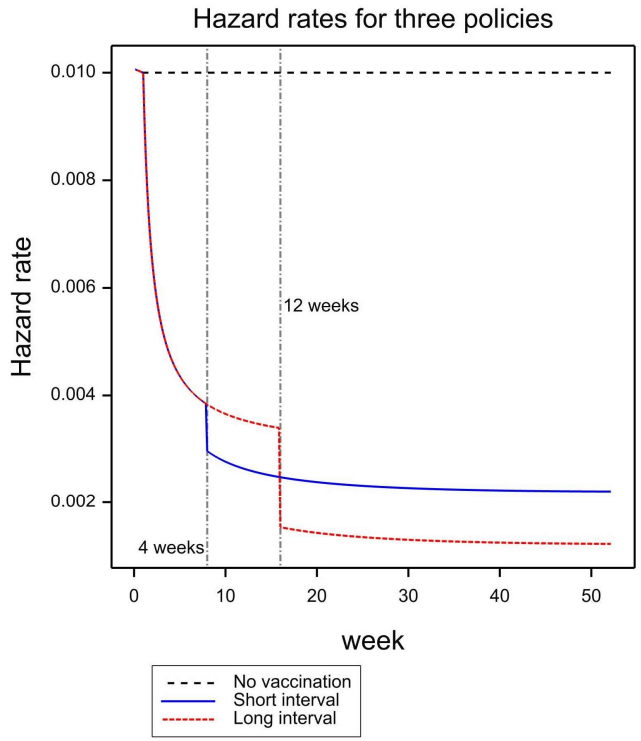
- Subjects who are chosen to be vaccinated are invited to attend a clinic to receive their vaccine.
- A team of health workers is assigned for vaccination and another team is assigned for assessing controls.
- Blood samples are collected by the vaccinating clinic.
- Subsequent blood samples (say after 28 days) are also collected in the vaccinating clinic.
- Samples are sent in batches to the laboratory to be analysed.
- Control subjects are visited by nurses at home to collect blood samples.

How auto-correlation can lead to clustering





What policy for vaccination?
Timing of the second jab



Conclusions

Report card

Lessons

Good thing done

- Some brilliant work by the life scientists
- Big trials done rapidly
- Regulators worked fast
- Subsequent roll out impressive

For discussion

- Pfizer's bizarre choice of prior distribution
- Oxford/AstraZeneca's unwise choice of allocation ratio
- Improbable success of analysis based on cases only?
- Importance of concurrent control
- Importance of using an appropriate scale