SARS-COV-2 Vaccine Trials What do we know and when do we know it?

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Why are we here?

- Four large ongoing vaccine trials
  - AstraZeneca, Janssen, Moderna, Pfizer
- All companies have made their protocols publicly available (this is great!)
- We all want a safe and effective vaccine as quickly as possible.

Outline

- What is their general trial design?
  - i.e. “what’s with these interim analyses?”
- What protections do these trials provide?
  - chance of false discovery
  - safety information
- Now that we know what happened (at least for a couple of them)…what did we learn?

Four trials by the numbers…

Sponsor	AstraZeneca	Janssen	Moderna	Pfizer
Overall Sample Size	30,000	60,000	30,000	44,000
Randomization Ratio (Trmt : Ctrl)	2:1	1:1	1:1	1:1
Show superiority to VE =	30%	30%	30%	30%
Maximal events	150	154 (?)	151	164
Powered for VE =	50%	60%	60%	60%
Statistical Method	Poisson regression (age as covariate)	Binomial on Event Split	Cox Proportional Hazards	Binomial on Event Split

Sample size

- Trials really need to see events. To see events, we need a large sample size.

- October back of the envelope…..In the USA
  - The current "new daily cases rate" is ~40,000
  - So in 100 days we expect to see 4,000,000 cases
  - About 1.25% of the population (320,000,000)

- With 30,000 patients
  - 15,000 per arm
  - 1.25% of 15,000 placebo is 187.5 events

Safety (Shorter Term)

- Short/mid term reactions to injections
  - samples size measures in terms of patients in trial, should be in the thousands even if events accrue rapidly
- These events should be well estimated

Safety (Long Term)

- A declaration of efficacy
  - does not stop the trial
  - patients are still followed up long term (2 yrs)
- However, at time of EUA, long term followup will be limited
- 2 months median followup
  - would prefer this said “for X participants”

Safety (Disease Severity)

- With 150-165 events, all trials monitor for disease severity
  - some tie this to success

- However, it is very hard to accurately estimate disease severity with these sample sizes

Interim Analyses

- All four trials have interim analyses
- At certain points, efficacy can be declared prior to the maximal event count
  - AstraZeneca, Moderna, Pfizer base these analyses on event counts
  - Janssen's are "at least weekly", but require certain conditions to start (more on this later…)

Interim Analyses

- All four plans protect against false claims
- If any vaccine is truly only 30% effective….
  - each trial has a 2.5% total chance of falsely declaring efficacy (total across all interims)
- Trials all obtain 85-90% power
  - limited chance of missing an effective vaccine

Interim Analysis Plans

	AstraZeneca	Janssen	Moderna	Pfizer
Maximal Events	150	154 (?)	151	164
Interim Events	75	see below	53,106	32,62,92,120
Alpha-spending (one-sided)	p<0.00155, p<0.0245 at final	SPRT* Weekly interims	p<0.0002, p<0.0073, p<0.0227 at final	Pr(VE>30%)>0.995 at interims Pr(VE>30%)>0.986 at final
Overall Type 1 Error Rate	2.5%	2.5%	2.5%	2.5%

Janssen has conditions on when interims start

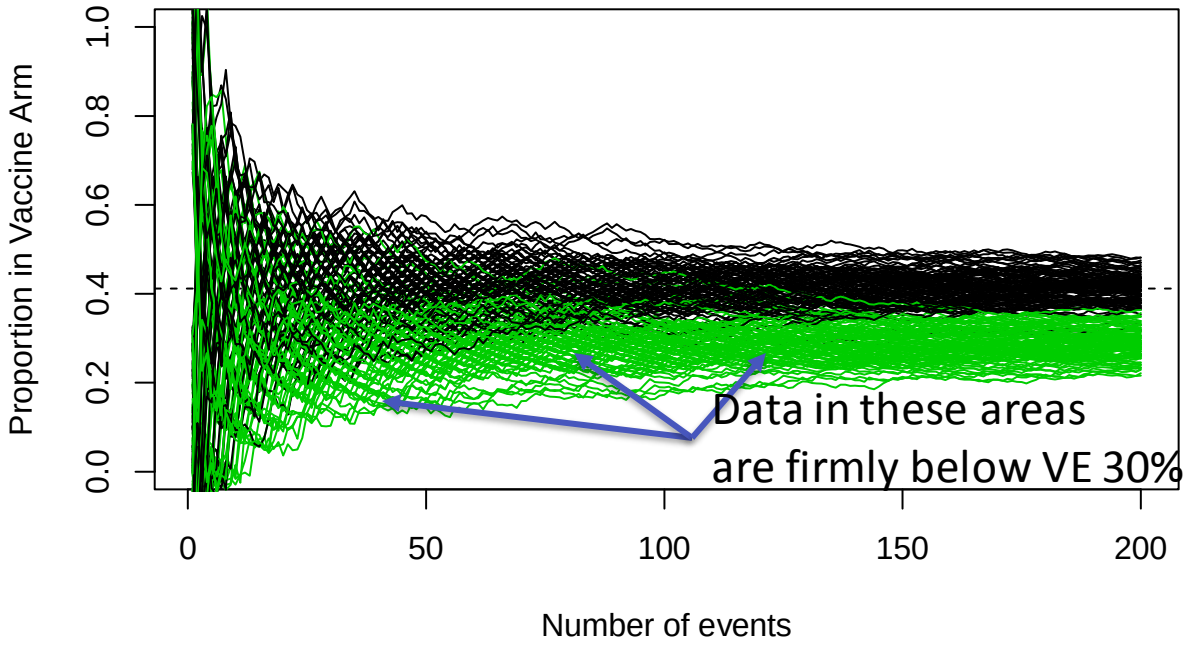
- 50% of patients with 2 months followup
- 20 COVID events (at least 5 severe, at least 6 >= 60 yrs old)

After that interims are weekly

If this occurs after 154 events, there is a single analysis when these conditions are met

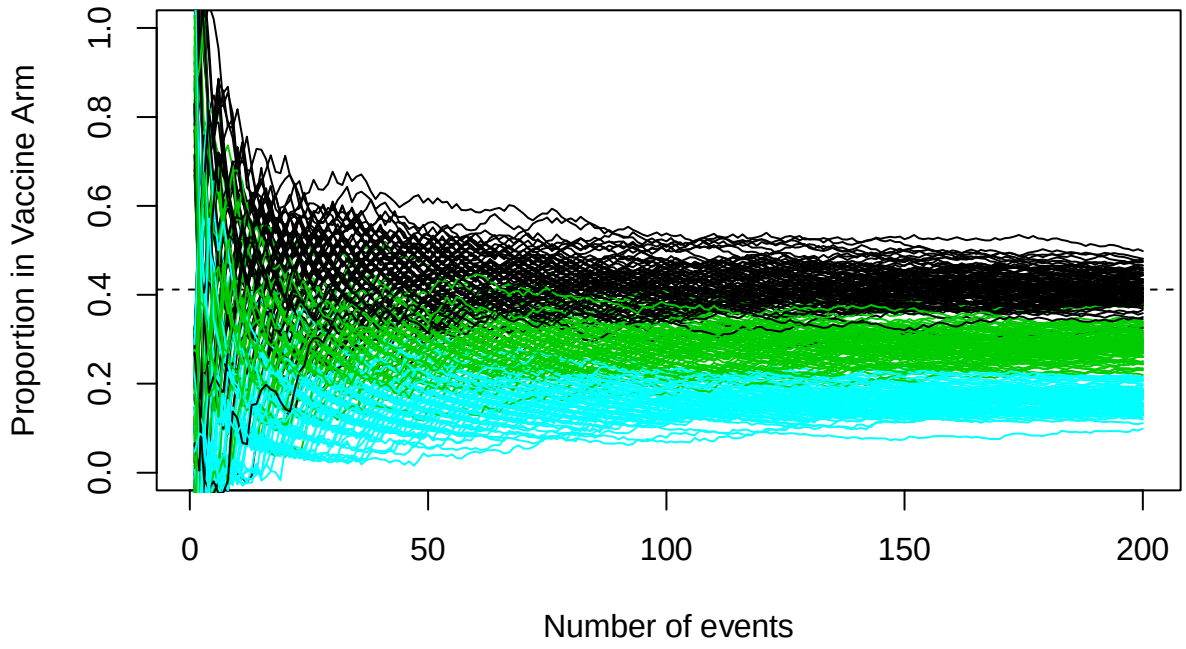
Lots of convincing interim data

Black = samples paths from 30% VE
Green = sample paths from 60% VE
While earlier time points present the possibility of black/green overlap, there are lots of results which are firmly good or firmly bad.



If VE=80%

A hugely effective vaccine would differentiate itself from the black VE=30% range very quickly.



Pfizer

Table 5. Interim Analysis Plan and Boundaries for Efficacy and Futility

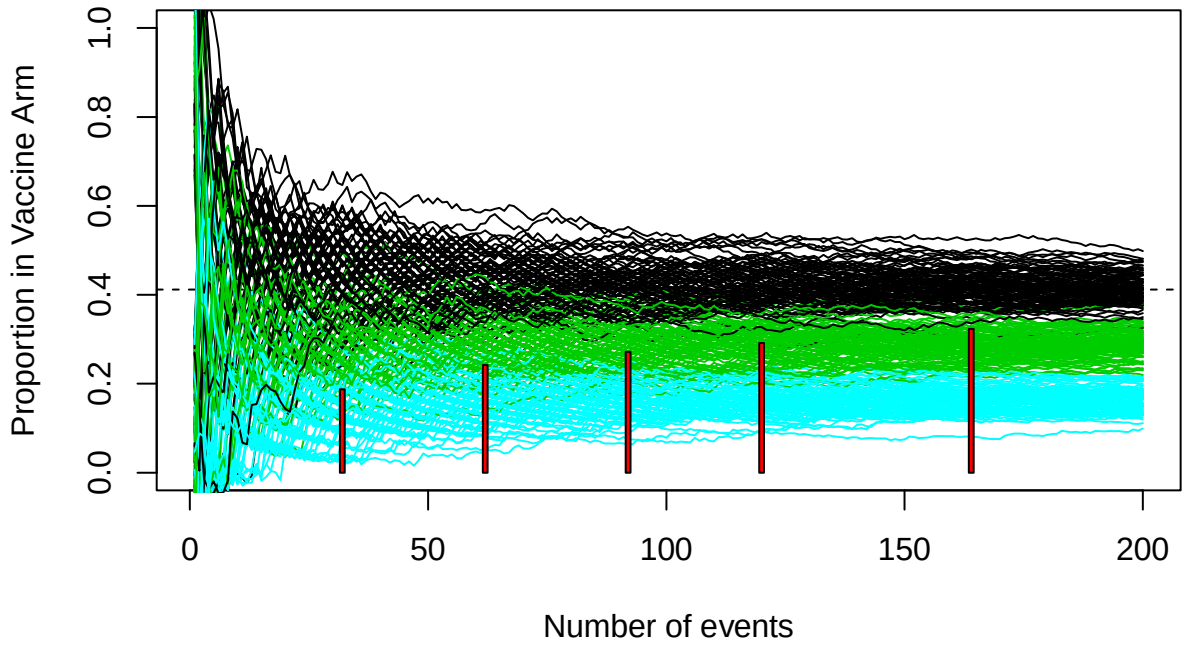
Analysis	Number of Cases	Success Criteria[a]	Futility Boundary
		VE Point Estimate (Case Split)	VE Point Estimate (Case Split)
IA1	32	76.9% (6:26)	11.8% (15:17)
IA2	62	68.1% (15:47)	27.8% (26:36)
IA3	92	62.7% (25:67)	38.6% (35:57)
IA4	120	58.8% (35:85)	N/A
Final	164	52.3% (53:111)	

Abbreviations: IA = interim analysis; N/A = not applicable; VE = vaccine efficacy.
Note: Case split = vaccine : placebo.
a. Interim efficacy claim: P(VE >30%|data) > 0.995; success at the final analysis: P(VE >30%|data) > 0.986.

Pfizer Efficacy Rules

Pfizer will stop and declare efficacy in the red rectangles

All are below the vast majority of black (VE=30%) paths.
They have a collective 2.5% type I error

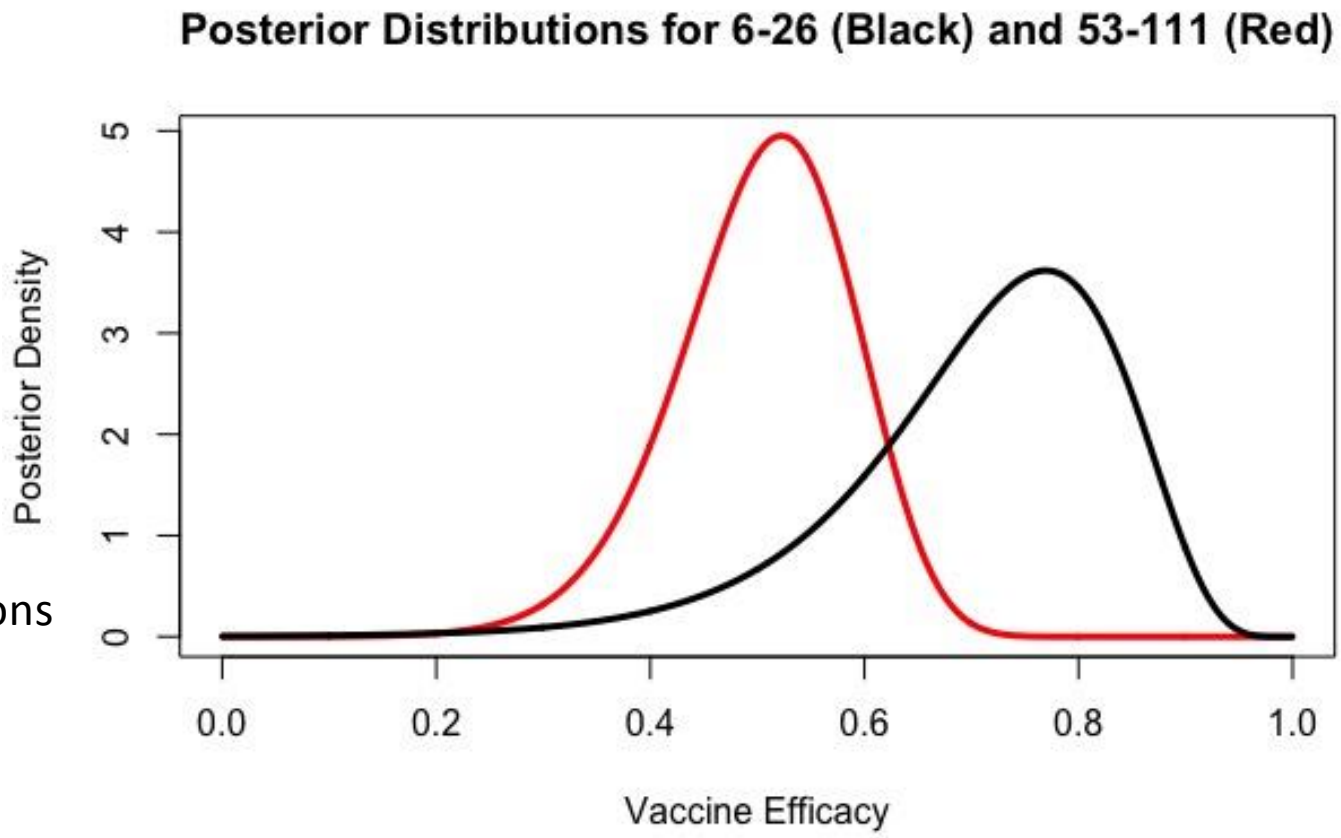


What is more compelling? 6-26 or 53-111

6-26 stochastically dominates 53-111

6-26 has more variability (we ”know” >30% but 60% and 90% are very different)

Should these questions be ”punted” in a public health emergency?



What about safety?

- Stopping at 32 (or 53, 62, or 75…or) does limit the amount of available safety data.

- For short term injection reactions
  - sample size is the number of patients, not events
  - if sponsor had enrolled thousands, even with 32 events this sample size could be quite large.

- For long term followup, the real question is the timing of the stop.

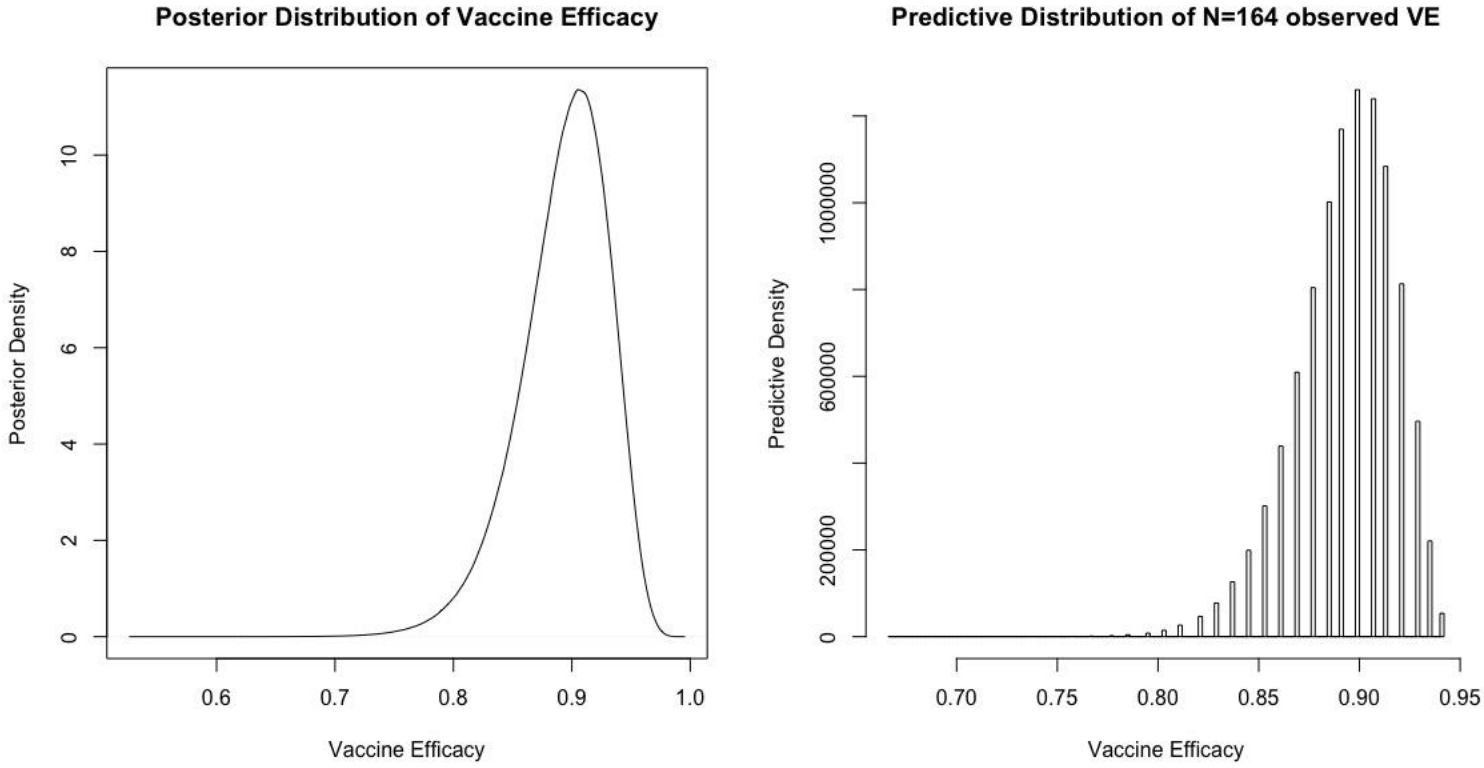
Long term followup

- Important to have sufficient followup
- Unclear what is “sufficient”
- Some discussion about having 50% or 100% of the patients followed up 2 months.
- Note diminishing returns of increasing N.
  - Suppose an AE rate was estimated 8% +/- 3.5%
  - Double the sample size, that becomes 8% +/- 2.5%

What happened?

- Pfizer bypassed first interim (FDA request for more extensive safety data)
- Upon agreement with FDA, Pfizer ran the second interim, but ended up with more than 62 events
  - there should be a plan somewhere
- VE ~ 90%, should be no controversy VE>30%

Predicting N=164 from interim



Was this right? It actually appears pessimistic….next result with over 164 events had 95% efficacy, perhaps indicating increasing immunity over time.