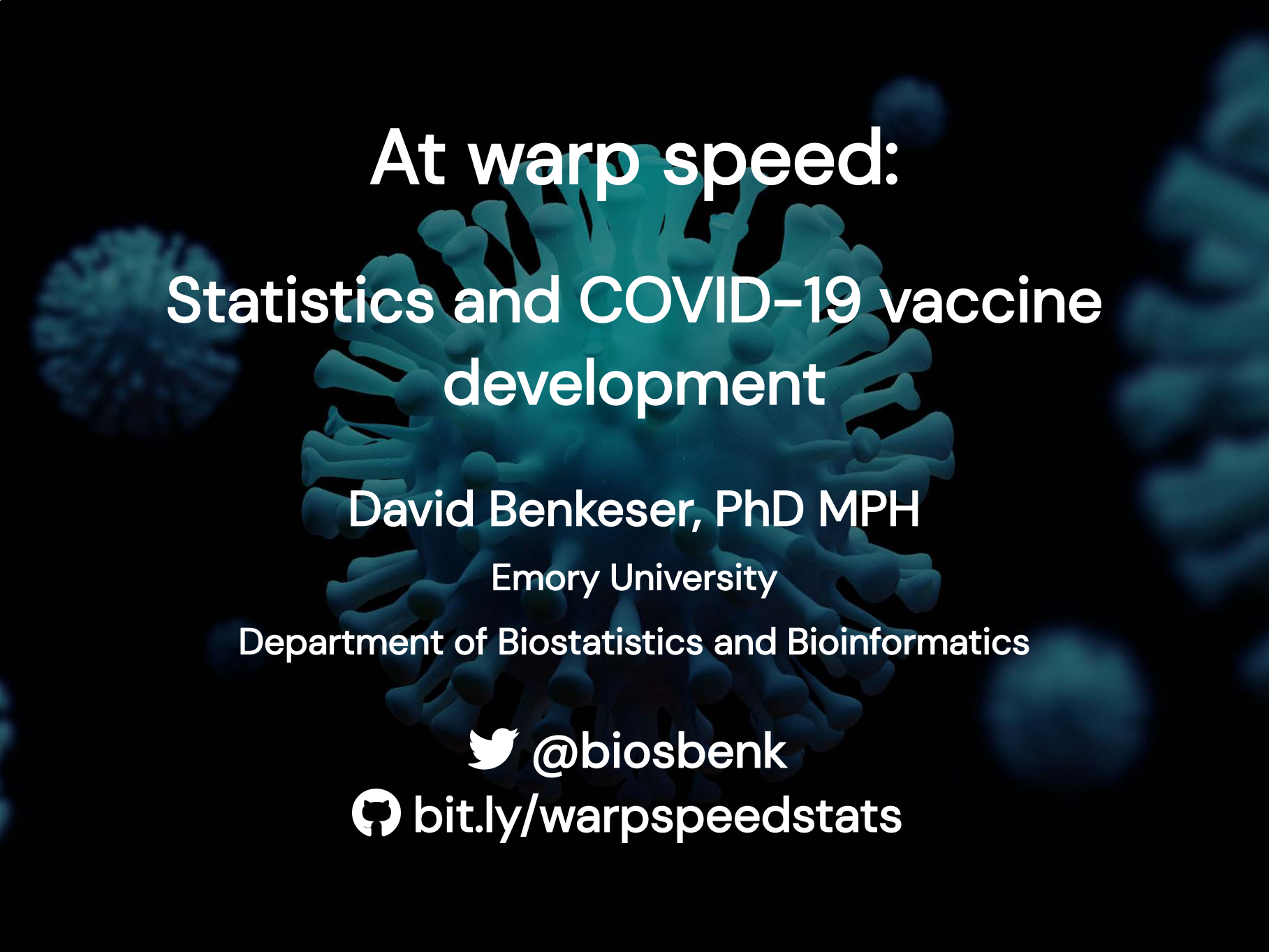

At warp speed:

Statistics and COVID-19 vaccine development

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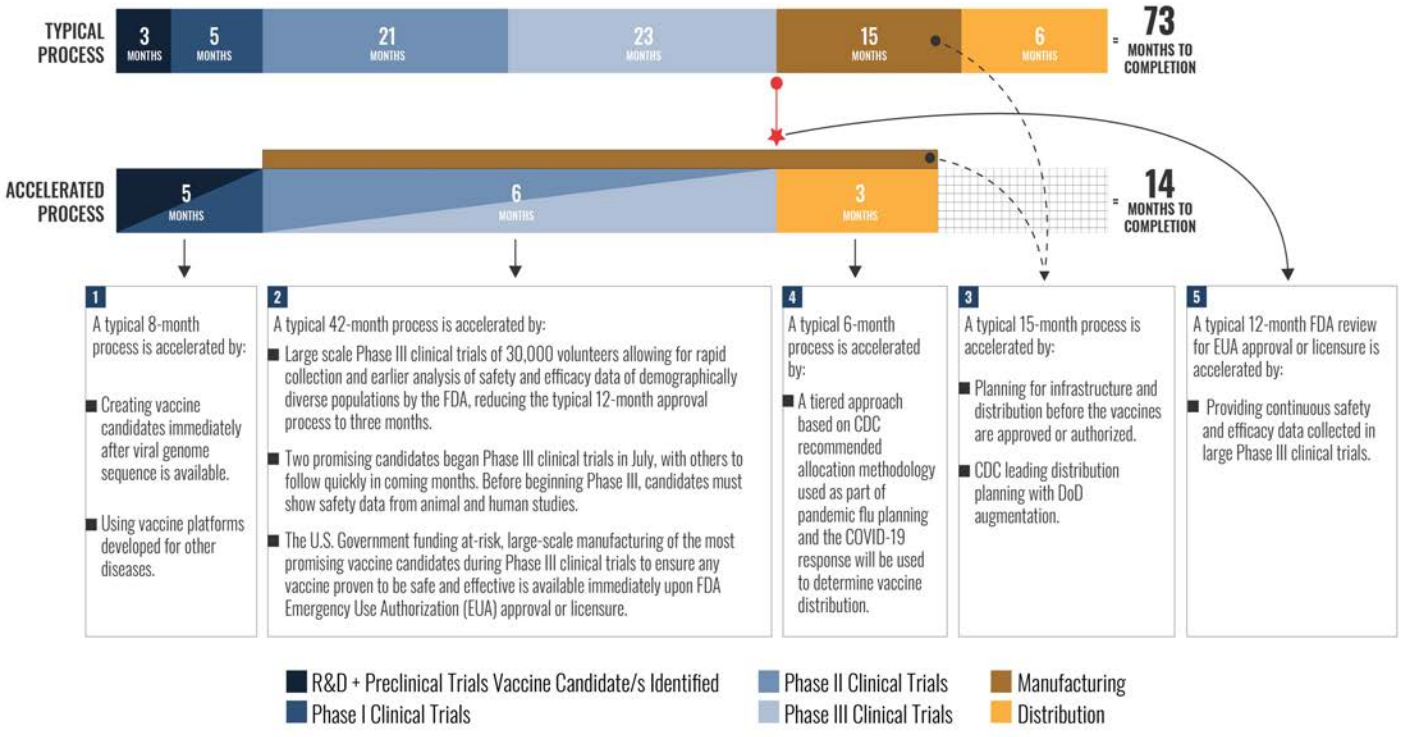
bit.ly/warpspeedstats

OPERATION WARP SPEED
ACCELERATED VACCINE PROCESS

MISSION: Deliver 300 million doses of safe and effective vaccine by 1 January 2021.

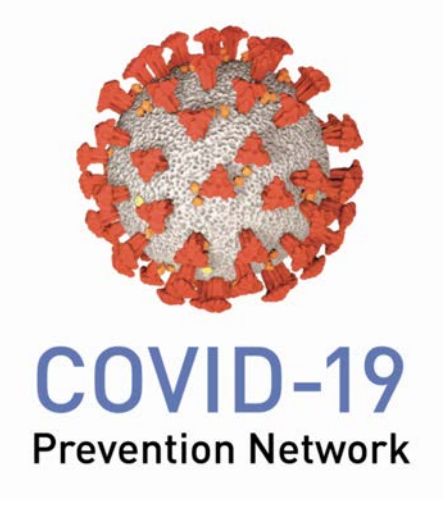


from DoD

COVID-19 Prevention Network

CoVPN was formed by NIAID to establish a unified clinical trial network for evaluating vaccines and monoclonal antibodies.

- pooling of resources across four existing trials networks
- clinical sites, laboratories, recruitment specialists, statisticians, ...



Statisticians advise on:

- primary trial design and analysis
- sequential efficacy monitoring
- safety monitoring
- DSMB/FDA comments
- immune correlates

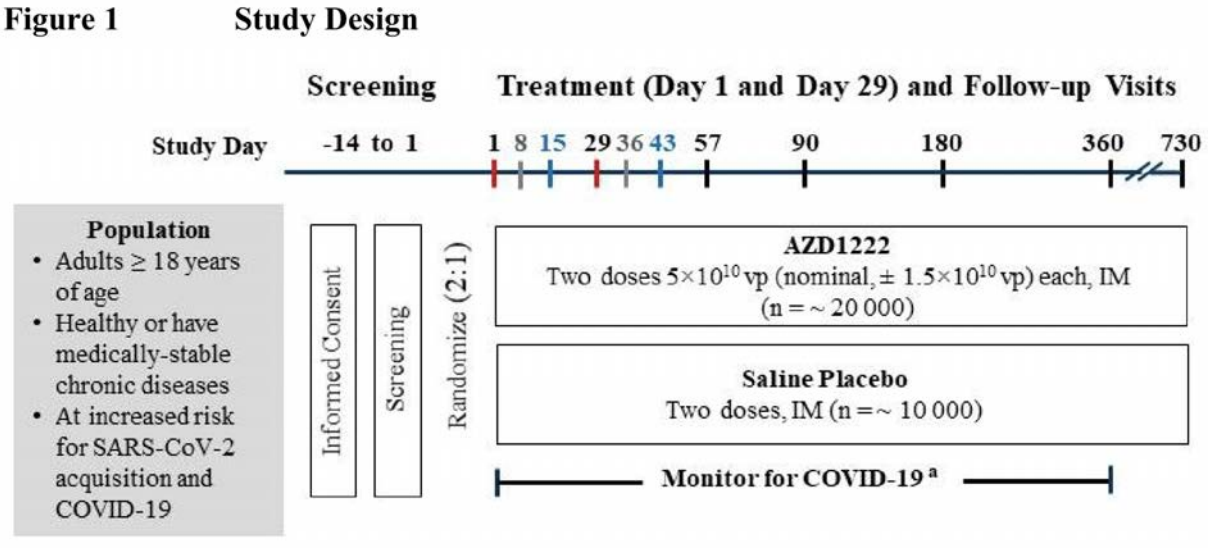
Design and analysis

AstraZeneca design

Trial protocols have (unusually) been made publicly available.

- Moderna, Pfizer, AZ, Janssen

All Phase III trials are largely similar to this:



- vaccine, immune response, phone call, clinic visit

What is primary hypothesis test?

Vaccine efficacy, VE, is the **percent reduction in relative risk** comparing vaccine to placebo.

$$\mathrm{VE} = 1 - \frac{\text{“risk” in vaccine}}{\text{“risk” in placebo}}$$

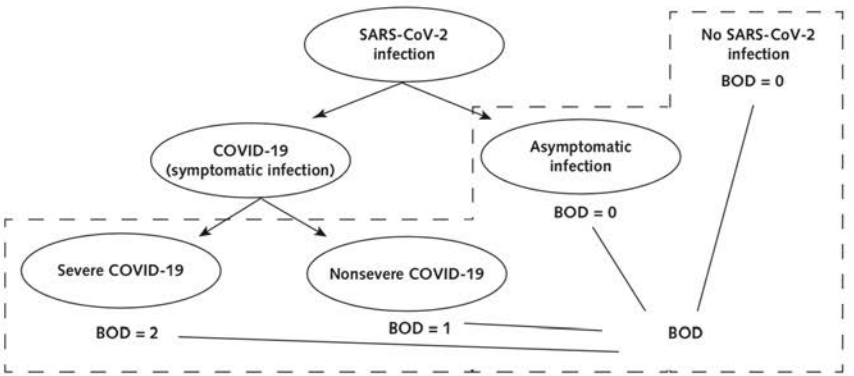
- “risk” of what? See next slides.
- “risk” quantified by hazard, cumulative incidence, incidence rate, ...
  - in rare event setting, all similar

FDA guidance (pg. 14) stipulates:

- a point estimate of VE for the primary endpoint of at least 50% **and**
- lower bound of an appropriately adjusted confidence interval >30%.
- overall type I error control for one-sided test at 2.5%.

What is the most relevant endpoint?

Figure 1. Clinical endpoint relationships, definitions, and example sampling scheme for diagnosed COVID-19 cases.



Clinical Endpoint	Definition
SARS-CoV-2 infection	Positive RNA PCR result or SARS-CoV-2 seroconversion*, whichever occurs first
COVID-19 (symptomatic infection)	Meeting a protocol-specified list of COVID-19 symptoms with virologic confirmation of SARS-CoV-2 infection (symptom triggered)
Asymptomatic infection	SARS-CoV-2 seroconversion* without prior diagnosis of the COVID-19 endpoint†
Severe COVID-19	COVID-19 endpoint with at least 1 protocol-specified severe disease event
Nonsevere COVID-19	COVID-19 endpoint with 0 protocol-specified severe disease events
BOD	Composite endpoint score of 0 for no COVID-19, 1 for nonsevere COVID-19, and 2 for severe COVID-19

Mehrotra et al (2020)

What is the most relevant endpoint?

SARS-CoV-2 infection

- + relevant to stemming spread, many infections will be observed
- – clinically relevant? measured coarsely in time; many false positives

COVID

- + more clinically relevant, reasonable number of cases expected
- – clinically relevant if symptoms are mild?

Severe COVID

- + most clinically relevant, a-priori highest expected efficacy
- – very few cases expected to be observed, longer evaluation needed

What is the most relevant endpoint?

Burden of disease (BOD)

- + more clinically relevant than COVID
- + lower power for vaccines of questionable benefit
- + power at least as high as COVID for likely vaccine profiles
- – best way to assign burden score? treating ordinal as continuous 🤷

Assumed VE, %		Statistical Power, %		
COVID-19	Severe COVID-19	Severe COVID-19	COVID-19	BOD
60	0	0	91	47
60	30	2	91	70
60	60	27	91	89
60	70	50	91	93
60	80	76	91	96
60	90	95	91	98

What is the most relevant endpoint?

FDA guidance (pg. 13) states **either COVID or SARS-CoV-2 infection** is an acceptable primary endpoint.

- OWS guidance to companies has been that **infection alone** is **not acceptable** as primary endpoint.

FDA guidance states companies, "should consider **powering efficacy trials** for formal hypothesis testing on a **severe COVID endpoint** [or] evaluate as a **secondary endpoint**."

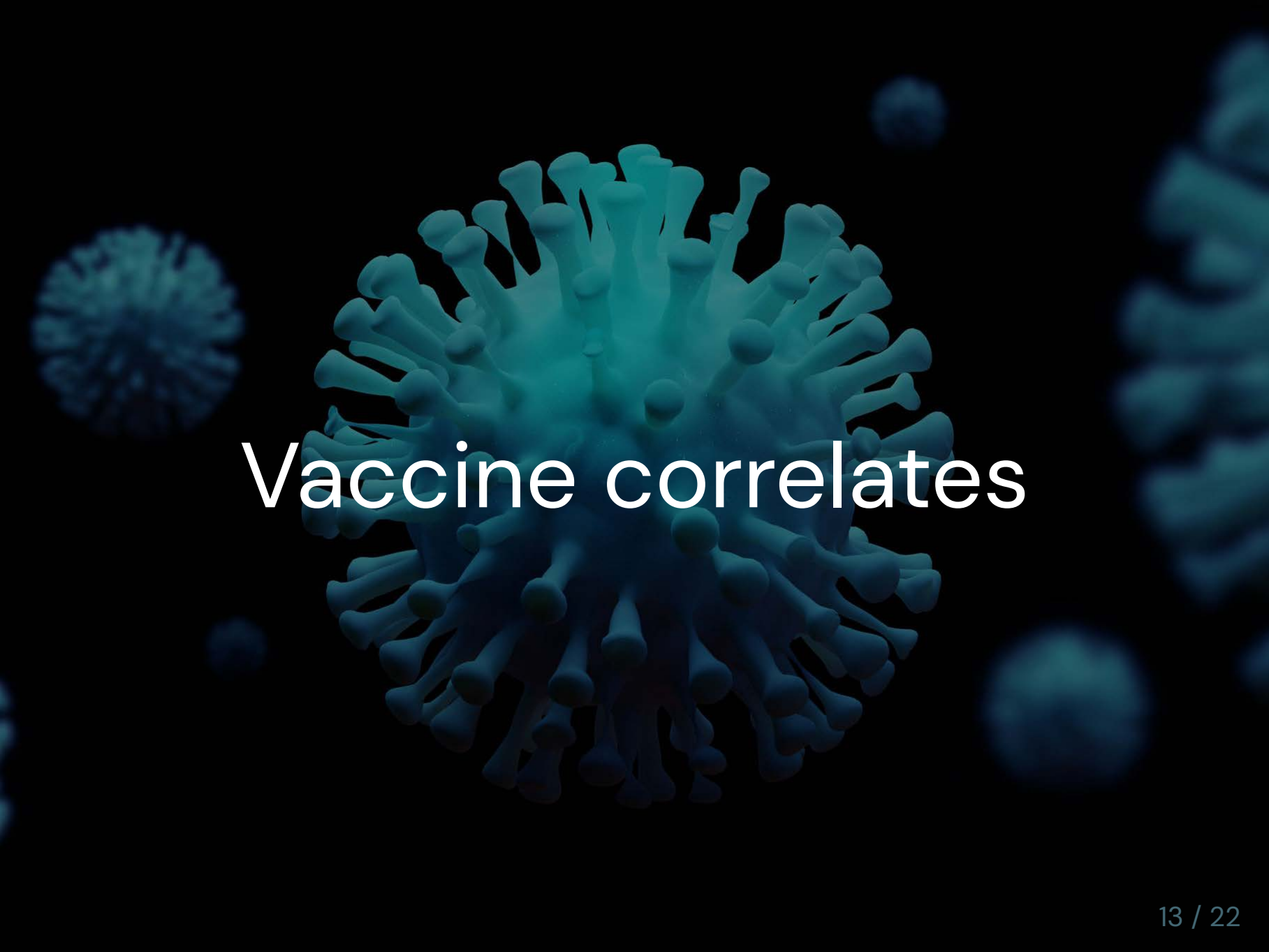
- Only Janssen so far is powering for severe COVID as primary.

Reported results

Results

Company	VE COVID (95% CI)	Cases (vax:placebo)	VE Severe (95% CI)	Cases (vax:placebo)
Pfizer/BioNTech	94.6 (90.0, 97.9)	170 (8:162)	88.9 (19.8, 99.7)	10 (1:9)
Moderna	94.1 (89.1, 97.0)	196 (11:185)	100.0 (86.9, 100.0)	30 (0:30)
Oxford/ AstraZeneca (low)	90.0 (63.9, 97.8)	33 (3:30)	100.0 (???, ???)	?? (0:??)
Oxford/ AstraZeneca (full)	61.9 (40.0, 76.5)	98 (27:71)	100.0 (???, ???)	?? (0:??)
Sputnik	91.7 (77.7, 97.4)	20 (4:16)	???? (???, ???)	?? (0:??)

VE COVID reported in press releases. CI roughly computed based on case splits.



Vaccine correlates

Correlates of risk/protection

Two, interrelated goals of correlates analysis are to

- identify/validate possible surrogate endpoints;
- understand protective mechanisms of vaccines.

If an immune correlate is established to reliably predict vaccine efficacy, then subsequent efficacy trials may use the CoP as the primary endpoint.

Accelerates approval of

- existing vaccines in different populations (e.g., children);
- new vaccines in the same class.

Correlates of risk/protection

Two levels of correlates analysis*:

Correlates of risk:

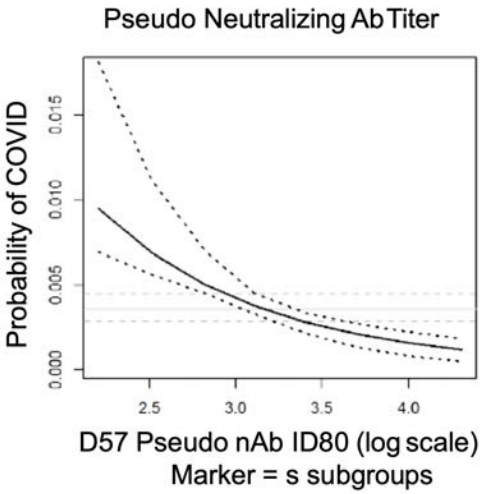
- Correlation of immune response in vaccine recipients with outcome
- Risk prediction
- Evaluates associative parameters

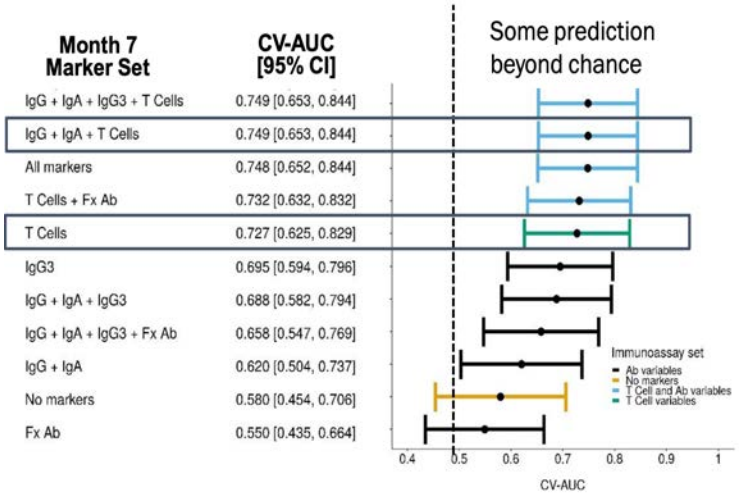
Correlates of protection

- Evaluate immune response's ability to predict vaccine efficacy
- Evaluates causal parameters

* Plotkin and Gilbert (2012), Qin et al (2007)

Correlates of risk





- Risk given immune response + baseline covariate adjustment
- E.g., Cox model

- Machine learning prediction using different sets of immune responses*.

* Neidich et al (2019)

Correlates of protection

Effect modifiers of VE

- How/does VE vary across subgroups defined by immune response?
- E.g., Juraska et al (2020)

Mediators of VE

- What percentage of VE is attributable to immune response?
- E.g., Cowling et al (2019)

Stochastic interventional VE

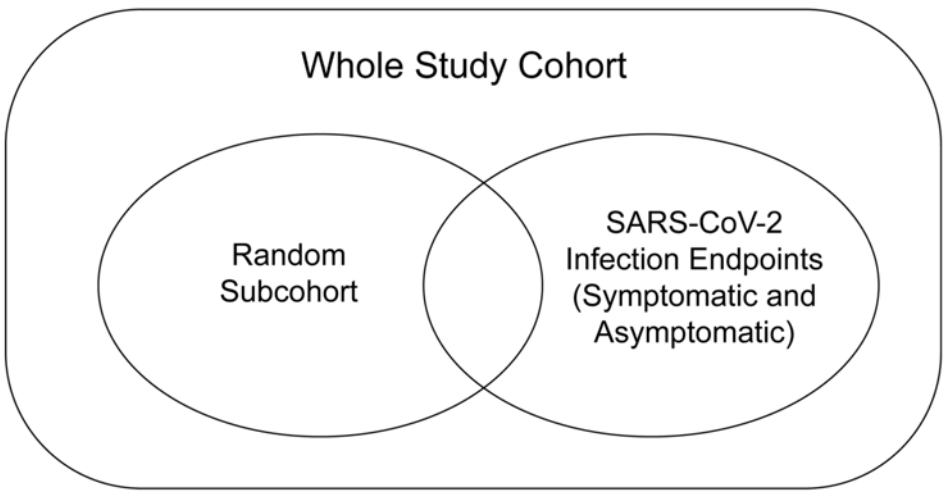
- How/would shifting the immune response distribution impact VE?
- Hejazi et al (2020)

Measuring correlates

Running assays on >30k samples is expensive and statistically unnecessary.

Instead we use a case-cohort design (Prentice, 1986) to measure immune responses in

- a stratified random subcohort (~1600 individuals)
- all SARS-CoV-2 endpoints



Statistical challenges

Estimation in two-phase designs

- Individuals who contract COVID may **differ from other participants**.
- Two-phase design over-samples these individuals.
- Augmented/inverse weighting approaches to **account for differences**.

Low case numbers due to highly effective vaccines

- Power for CoP analysis driven by **vaccine breakthroughs**.
- There were only 11 breakthroughs in Moderna!
- Need to be **judicious** in which analyses are performed.
- Ultimately, **establishment of correlate** will need to additionally draw from **other sources of data**.

Transparency and reproducibility

CoVPN statisticians are committed to open science.

An in-progress, version-controlled SAP is available for review.

An **open-source R package** is being developed to implement methods involved in the SAP.

- Reproducible reports using R Markdown
- Vignettes including analysis of simulated data

Release of package and first correlates reports expected in **early 2021**.

Concluding thoughts

Can we **trust** the vaccine development process?

- Unequivocally, yes. Safety of vaccines is **aggressively monitored**.

Efficacy results thus far are **overwhelmingly positive**.

- I am still in shock.

The story is not (close to) over. **There is still much to do and learn**!

- Community outreach/education to increase uptake
- Durability of vaccines
- Efficacy against infection/transmissibility
- Designs when placebo controls are not possible/ethical
- ...

Amazing statisticians

Leadership

- Dean Follmann (NIAID)
- Yonghong Gao (BARDA)
- Peter Gilbert (FHCRC, UW)

NIAID

- Martha Nason
- Mike Fay
- NIAID Biostatistics

CoVPN

- Alex Luedtke (UW)
- Marco Carone (UW)
- Iván Díaz (Weill-Cornell)
- Nima Hejazi (Berkeley)
- many others!

Fred Hutch

- Holly Janes
- Youyi Fong
- Yunda Huang
- Michal Juraska
- Ying Huang
- Ollivier Hyrien
- many others!