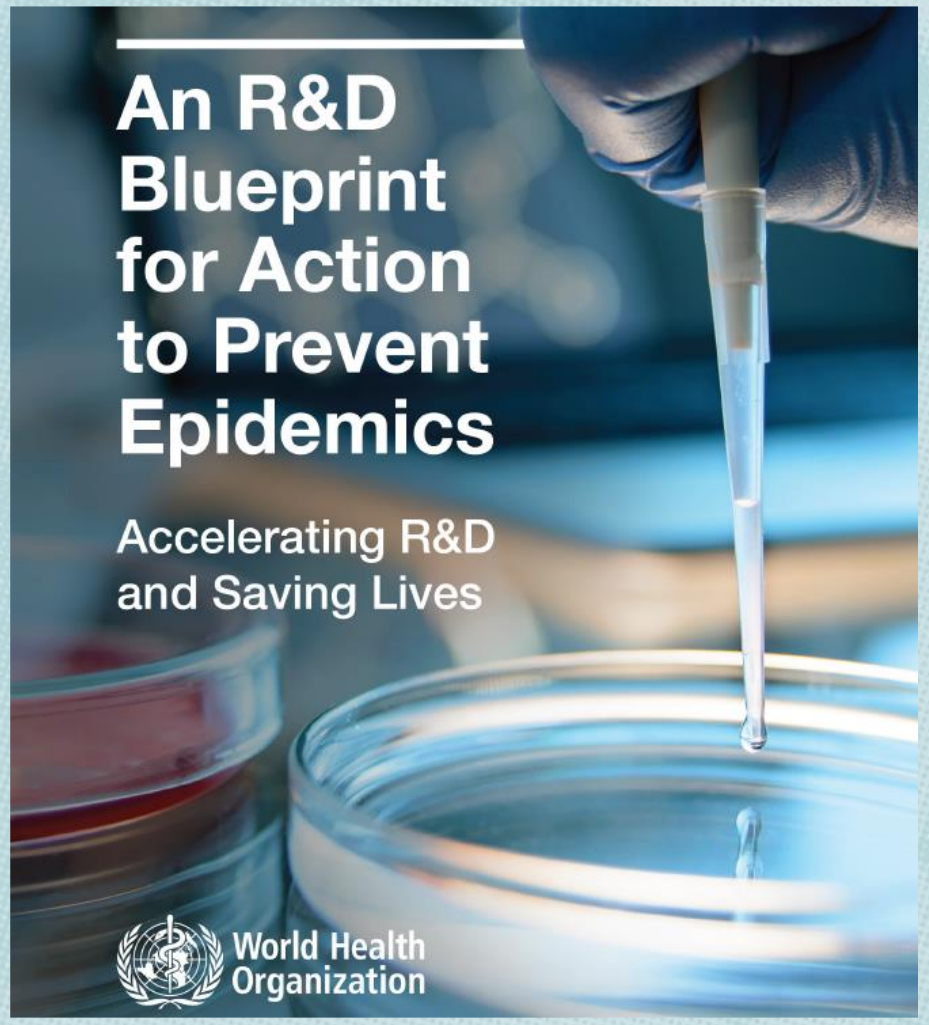
An Overview of COVID-19 Vaccine Efficacy Trials

NISS-Merck Meet Up
January 13, 2021

Natalie Dean
Department of Biostatistics
PHHP/COM
Emerging Pathogens Institute
University of Florida
nataliedean@ufl.edu

VACCINE BASICS

WHO R&D Blueprint



C

Developing norms & standards

1. Clinical trial designs
2. Data & sample sharing

Prioritized pathogens

- Crimean Congo Hemorrhagic Fever (CCHF)
- Ebola and Marburg virus disease
- Lassa fever
- MERS-CoV and SARS
- Nipah and henipaviral diseases
- Rift Valley Fever (RVF)
- Zika
- Disease X

Expectations for COVID-19 vaccines

SCIENCE TRANSLATIONAL MEDICINE | PERSPECTIVE

VACCINES

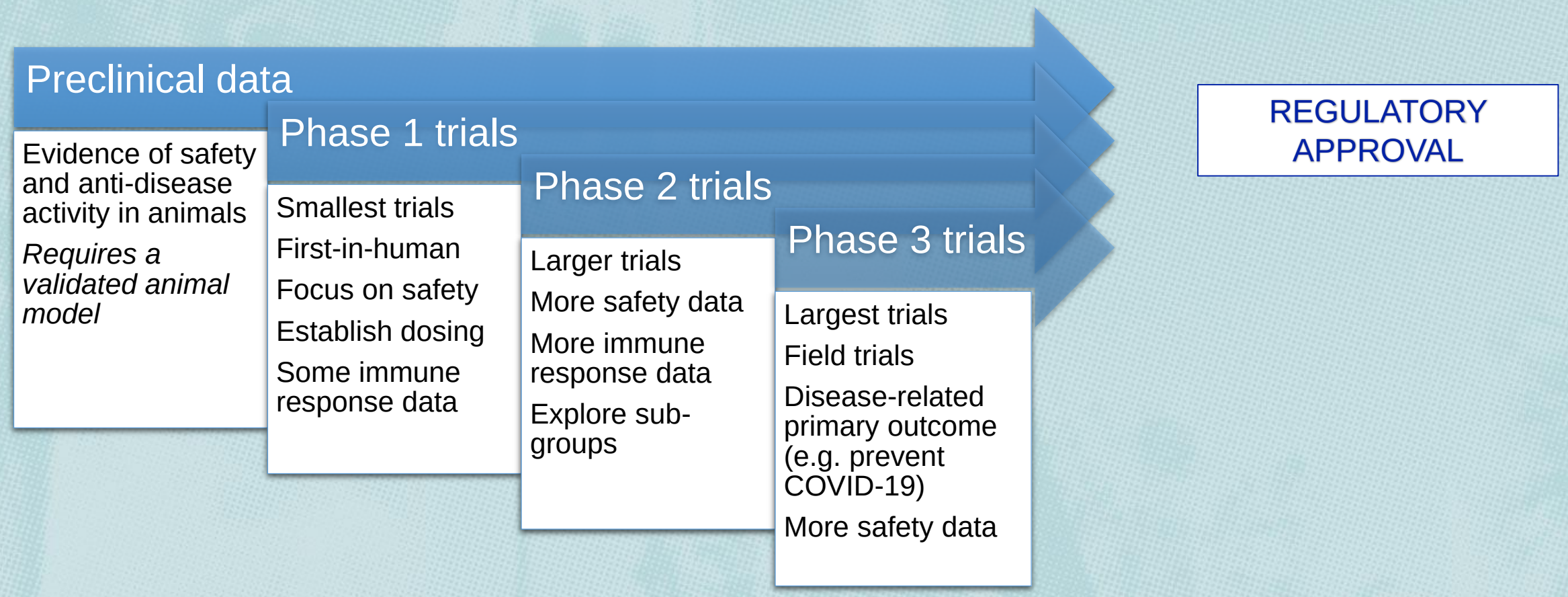
Design of vaccine efficacy trials during public health emergencies

Natalie E. Dean[1]*, Pierre-Stéphane Gsell[2], Ron Brookmeyer[3], Victor De Gruttola[4], Christl A. Donnelly[5,6], M. Elizabeth Halloran[7,8], Momodou Jasseh[9], Martha Nason[10], Ximena Riveros[2], Conall H. Watson[11], Ana Maria Henao-Restrepo[2], Ira M. Longini[1]*

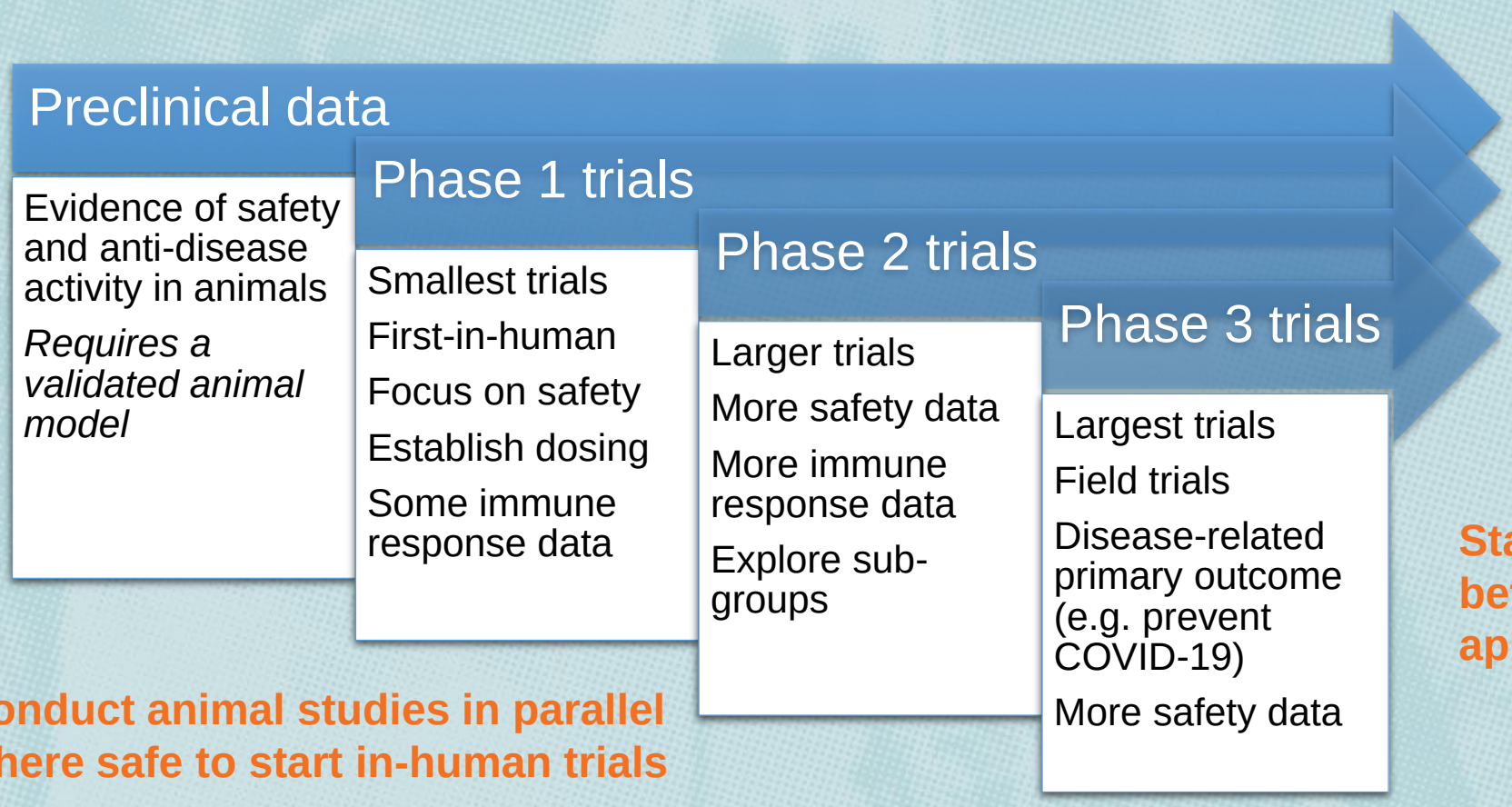
- "*The principal goal of a vaccine efficacy trial is to obtain efficacy and effectiveness data that can support broader use of a vaccine under a defined regulatory framework.*"
- Intended use for COVID-19: billions vaccinated

Dean et al. 2019 https://stm.sciencemag.org/content/11/499/eaat0360.abstract

Regulatory pathway for vaccines



Accelerating this pathway during a pandemic



Accelerated review process
Emergency Use Authorization instead of full licensure

REGULATORY APPROVAL

Start scaling up manufacturing before receiving regulatory approval

Conduct animal studies in parallel where safe to start in-human trials

Start planning subsequent steps before the prior step is completed

Shorter duration of follow-up than in a traditional trial

COVID-19 vaccine platforms

Over 100 vaccine candidates currently in development, utilizing a range of vaccine platforms

Table: Summary of general attributes

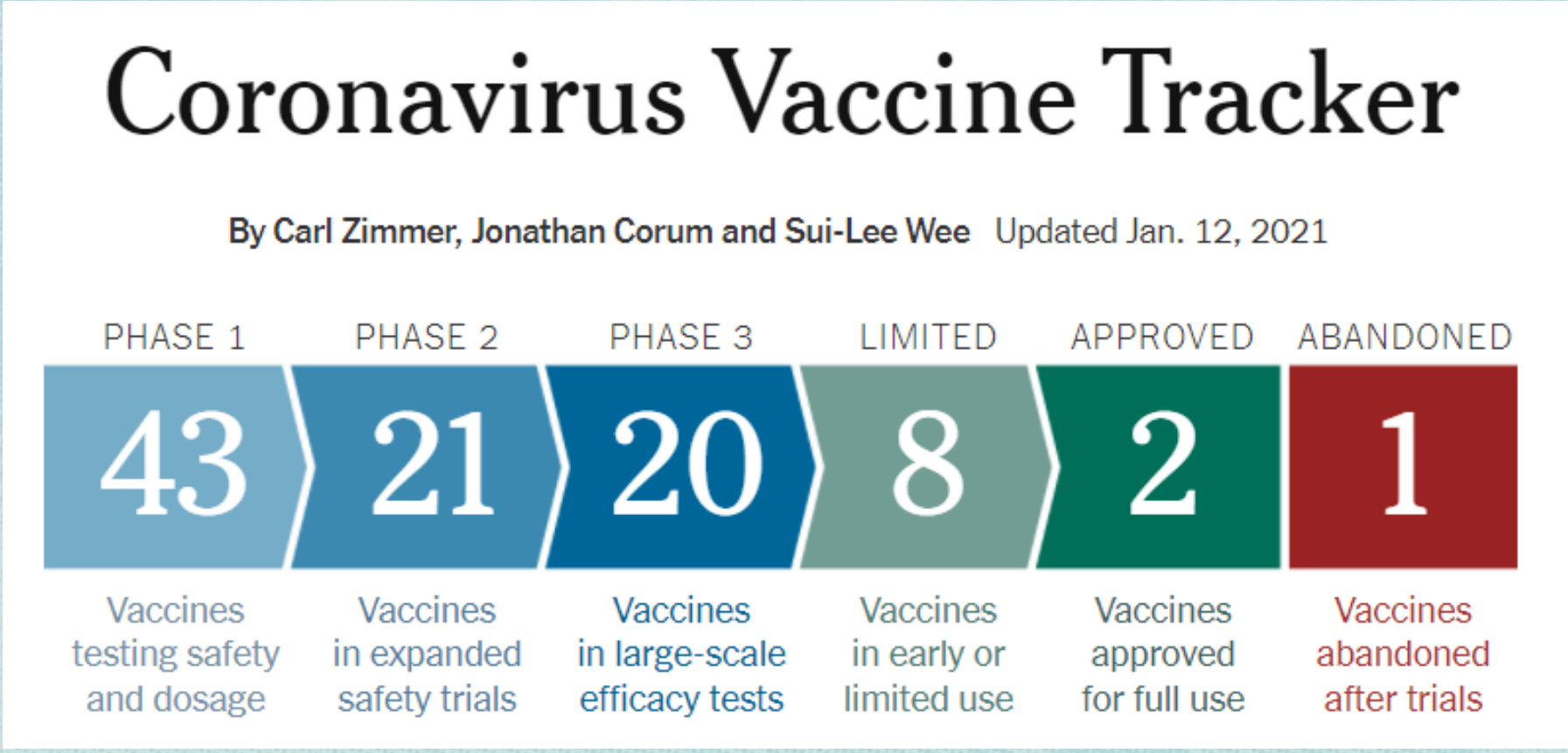
	Single dose	Licensed platform	Fast to develop	*Examples*
RNA			✓✓	BioNTech/Pfizer, Moderna
DNA			✓✓	Inovio
Non replicating vector	✓		✓	Gamaleya, Ozford/AZ, Janssen
Inactivated		✓	✓	Sinopharm, Bharat Biotech
Live attenuated	✓	✓		Codagenix
Replicating viral vector	✓	✓	✓	Merck
Protein subunit		✓	✓	Novavax

Modified from Lurie et al. (2020) *NEJM*

https://covid19.trackvaccines.org/vaccines/

UF

Tracking vaccines in the pipeline



https://www.nytimes.com/interactive/2020/science/coronavirus-vaccine-tracker.html

Key features of COVID-19 trials

- Adult participants (16+ or 18+)
  - Including high-risk groups (elderly adults, people with comorbidities)
- Individual randomization
  - Active vaccine vs. placebo
- Large trials
  - Tens of thousands of participants across many locations, countries
- Trials are EVENT-DRIVEN
  - The amount of efficacy data we need depends upon the number of cases we observe

UF

What is a successful vaccine?

- Efficacy = 1 – [“risk” in vaccine]/[“risk” in placebo]
- 50% efficacy against disease or infection
- Rule out a lower confidence bound of 30%
  - e.g. 95% CI (0.35, 0.85) successful
  - e.g. 95% CI (0.25, 0.75) not successful
- *Prevent the approval of weakly effective vaccines*
  - Divert resources
  - Lead to riskier behavior
  - Jeopardize evaluation of future vaccines
  - Erode public confidence in the process

Development and Licensure of Vaccines to Prevent COVID-19

Guidance for Industry

COMMENT | VOLUME 396, ISSUE 10253, P741-743, SEPTEMBER 12, 2020

COVID-19 vaccine trials should seek worthwhile efficacy

Philip Krause • Thomas R Fleming • Ira Longini • Ana Maria Henao-Restrepo • Richard Peto • for the World Health Organization Solidarity Vaccines Trial Expert Group † • Show footnotes

Published: August 27, 2020 • DOI: https://doi.org/10.1016/S0140-6736(20)31821-3 • Check for updates

https://www.fda.gov/regulatory-information/search-fda-guidance-documents/development-and-licensure-vaccines-prevent-covid-19

Krause et al. Lancet 2020 https://doi.org/10.1016/S0140-6736(20)31821-3

Selecting the primary endpoint

- SARS-CoV-2 infection
  - (+) Relevant to stemming spread. Many infections will be observed.
  - (-) Clinical relevance unclear. Measured coarsely in time. Many false positives.
- COVID of any severity
  - (+) 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.

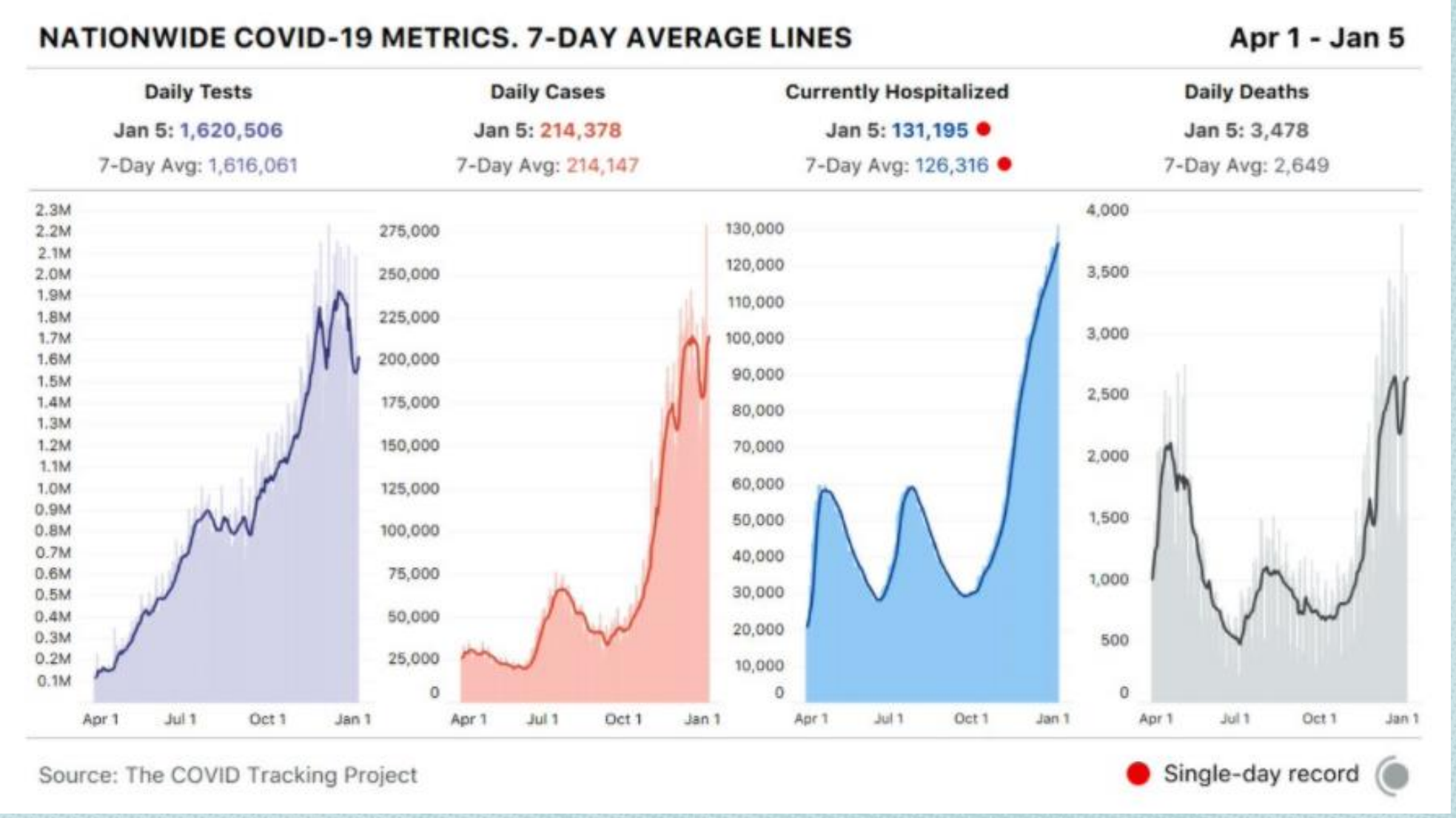
Slide from David Benkeser

UF

How long does it take to tell if the vaccine works?

- Target number of events is ~150 cases of PCR-confirmed, **symptomatic** COVID
- These events must occur more than 7 (or 14) days after the second dose to be counted
  - This excludes people who are infected before receiving the full vaccine
- *How long it takes to accrue this data depends upon how transmission is ongoing….*

How long does it take to tell if the vaccine works?



Follow up for safety

- "*FDA guidance recommends that data from phase 3 studies to support an EUA … include a median follow-up duration of at least 2 months after completion of the full vaccination regimen*" – Krause & Gruber
- EUA: "known and potential benefits of a product outweigh its known and potential risks"
- "*Adverse events considered plausibly linked to vaccination generally start within 6 weeks after vaccine receipt*"
- Balances the need for long-term safety data with the need for a vaccine to address the current pandemic

Krause & Gruber (2020) *NEJM,* DOI: 10.1056/NEJMp2031373

STATUS UPDATE

Status update

RNA

BioNTech/Pfizer

BNT162b2

Approved in 48 countries

3 trials in 6 countries

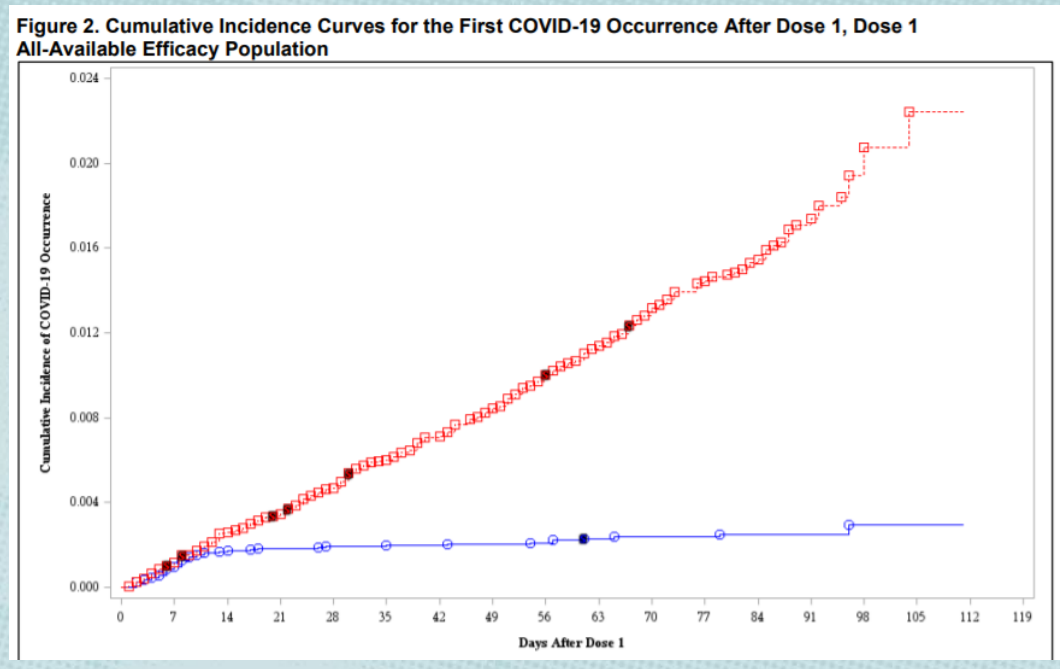


Table 6. Final Analysis of Efficacy of BNT162b2 Against Confirmed COVID-19 From 7 Days After Dose 2 in Participants Without Evidence of Prior SARS-CoV-2 Infection - Evaluable Efficacy Population

Pre-specified Age Group	BNT162b2 N[a] = 18198 Cases n1[b] Surveillance Time[c] (n2[d])	Placebo N[a] =18325 Cases n1[b] Surveillance Time[c] (n2[d])	Vaccine Efficacy % (95% CI)	Met Predefined Success Criterion*
All participants	8 2.214 (17411)	162 2.222 (17511)	95.0 (90.3, 97.6)[e]	Yes
16 to 55 years	5 1.234 (9897)	114 1.239 (9955)	95.6 (89.4, 98.6)[f]	NA
> 55 years and older	3 0.980 (7500)	48 0.983 (7543)	93.7 (80.6, 98.8)[f]	NA

Polack et al. (2020) *NEJM*

https://covid19.trackvaccines.org/

https://www.fda.gov/media/144245/download

Status update

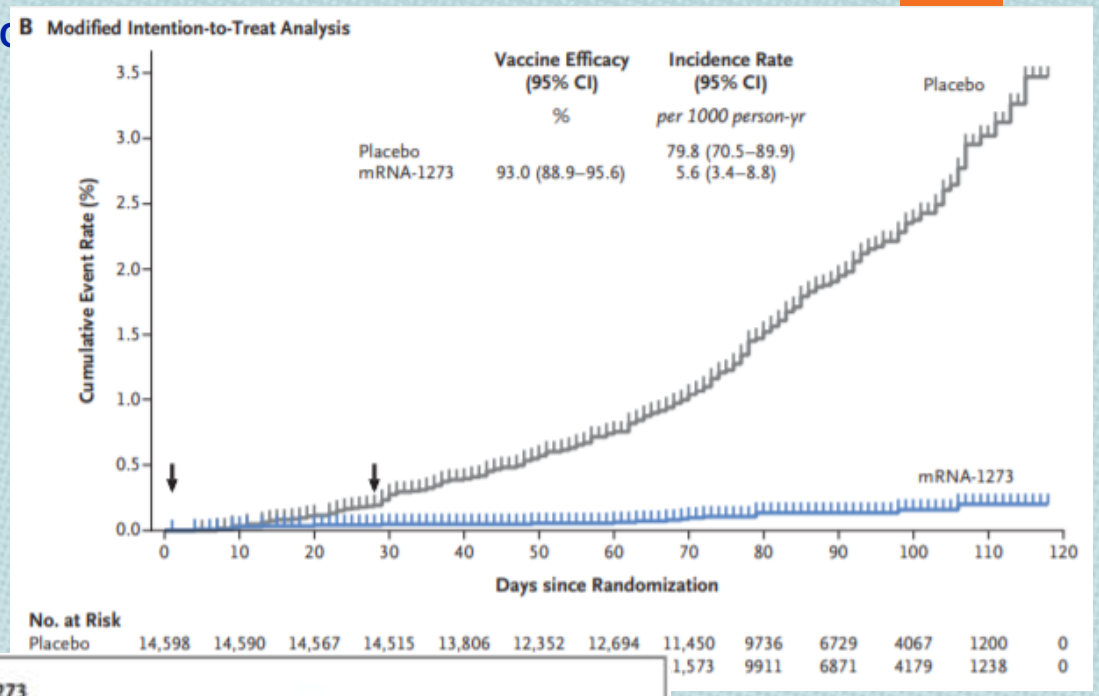
RNA

Moderna

mRNA-1273

Approved in 34 countries

5 trials in 1 country



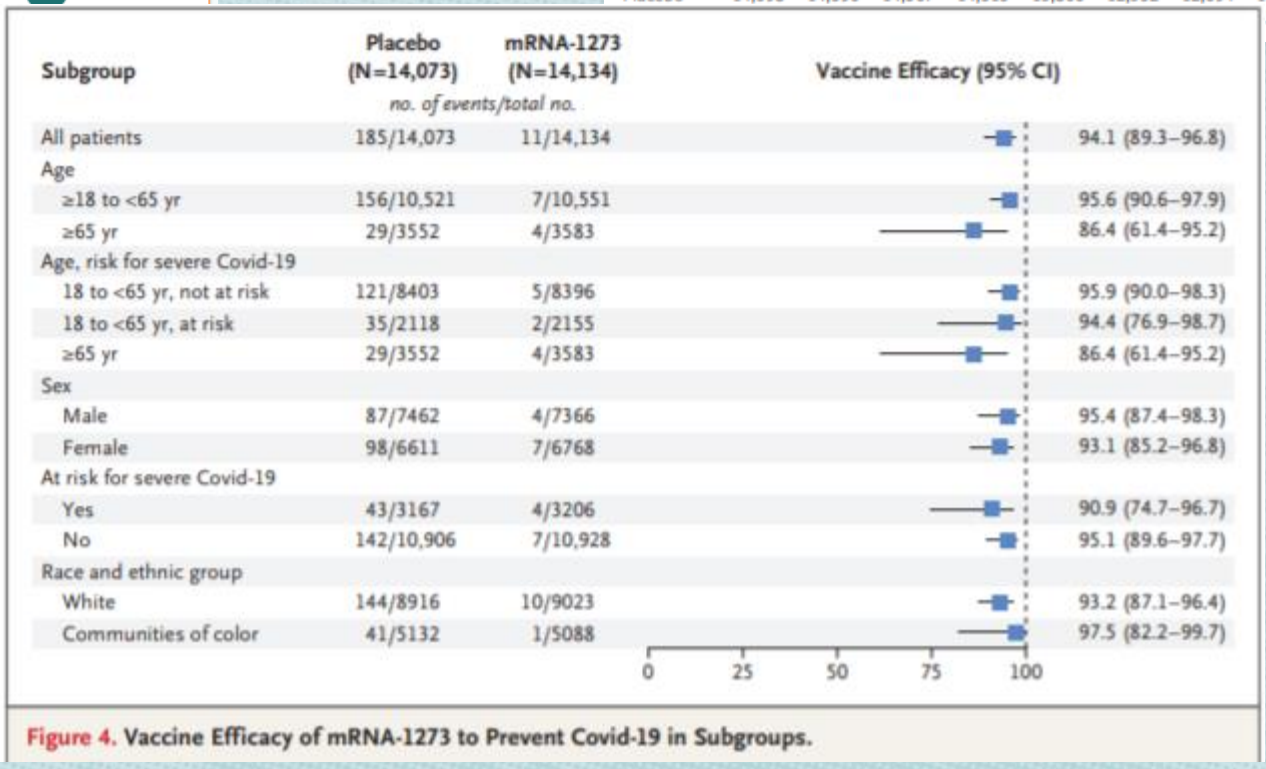


Figure 4. Vaccine Efficacy of mRNA-1273 to Prevent Covid-19 in Subgroups.

Baden et al. (2020) *NEJM*

https://covid19.trackvaccines.org/

UF

Status update

Non Replicating Viral Vector

Articles

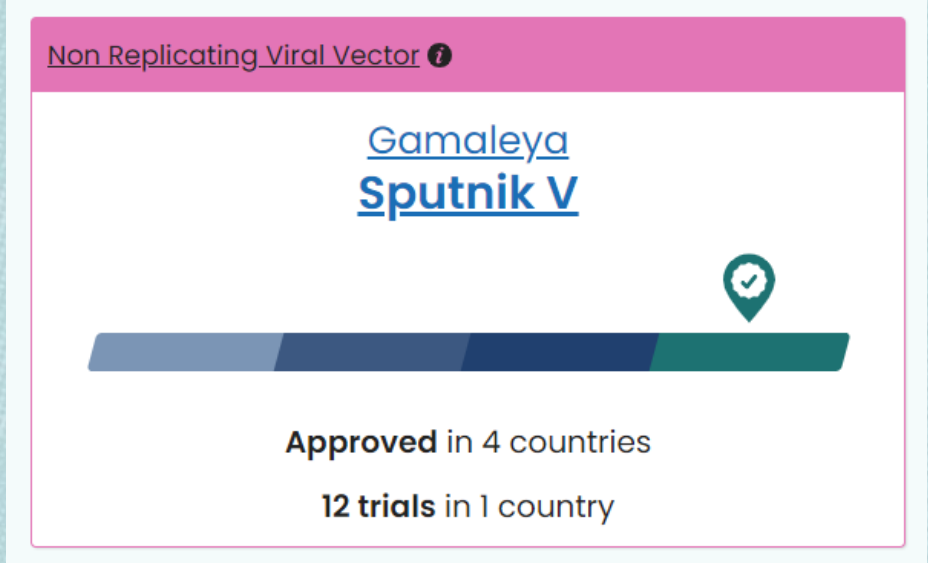
Safety and efficacy of the ChAdOx1 nCoV-19 vaccine (AZD1222) against

	Total number of cases	ChAdOx1 nCoV-19		Control		Vaccine efficacy (CI*)
		n/N (%)	Incidence rate per 1000 person-years (person-days of follow-up)	n/N (%)	Incidence rate per 1000 person-years (person-days of follow-up)	
All LD/SD and SD/SD recipients	131	30/5807 (0·5%)	44·1 (248 299)	101/5829 (1·7%)	149·2 (247 228)	70·4% (54·8 to 80·6)†
COV002 (UK)	86	18/3744 (0·5%)	38·6 (170 369)	68/3804 (1·8%)	145·7 (170 448)	73·5% (55·5 to 84·2)
LD/SD recipients	33	3/1367 (0·2%)	14·9 (73 313)	30/1374 (2·2%)	150·2 (72 949)	90·0% (67·4 to 97·0)‡§
SD/SD recipients	53	15/2377 (0·6%)	56·4 (97 056)	38/2430 (1·6%)	142·4 (97 499)	60·3% (28·0 to 78·2)
COV003 (Brazil; all SD/SD)	45	12/2063 (0·6%)	56·2 (77 930)	33/2025 (1·6%)	157·0 (76 780)	64·2% (30·7 to 81·5)‡
All SD/SD recipients	98	27/4440 (0·6%)	56·4 (174 986)	71/4455 (1·6%)	148·8 (174 279)	62·1% (41·0 to 75·7)

https://covid19.trackvaccines.org/

https://www.sciencedirect.com/science/article/pii/S0140673620326611?via%3Dihub

Status update



Reports that the Phase 3 trial reached its final total of 78 cases

Estimated vaccine efficacy was 91.4%

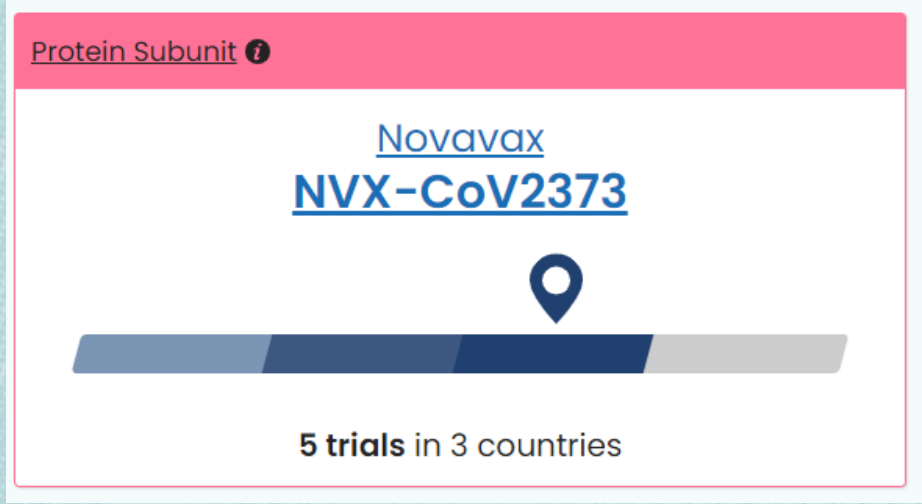
20 of the 78 cases were severe, and all were in the placebo group

AstraZeneca is partnering with Gamaleya to see if combining their vaccines would increase the efficacy of the Oxford vaccine

https://covid19.trackvaccines.org/

https://www.nytimes.com/interactive/2021/health/gamaleya-covid-19-vaccine.html

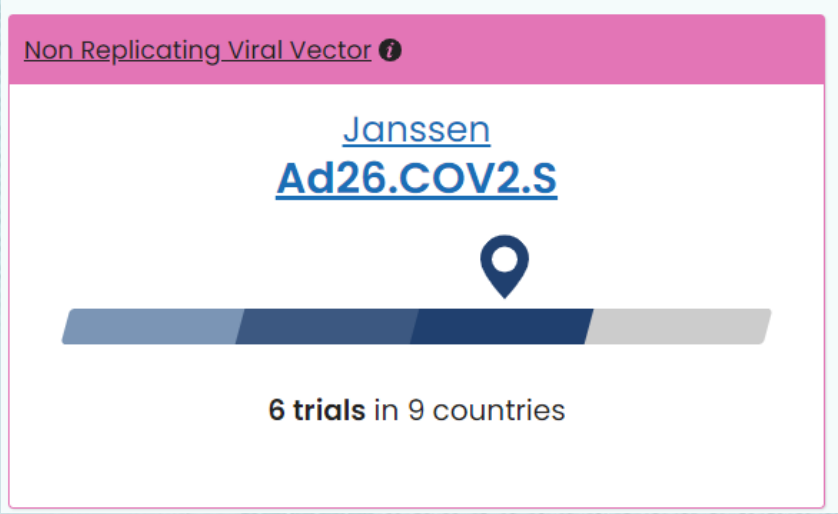
Status update



South African Phase IIb trial likely to reveal results within the next two weeks

UK trial fully enrolled

US/Mexico trial launched

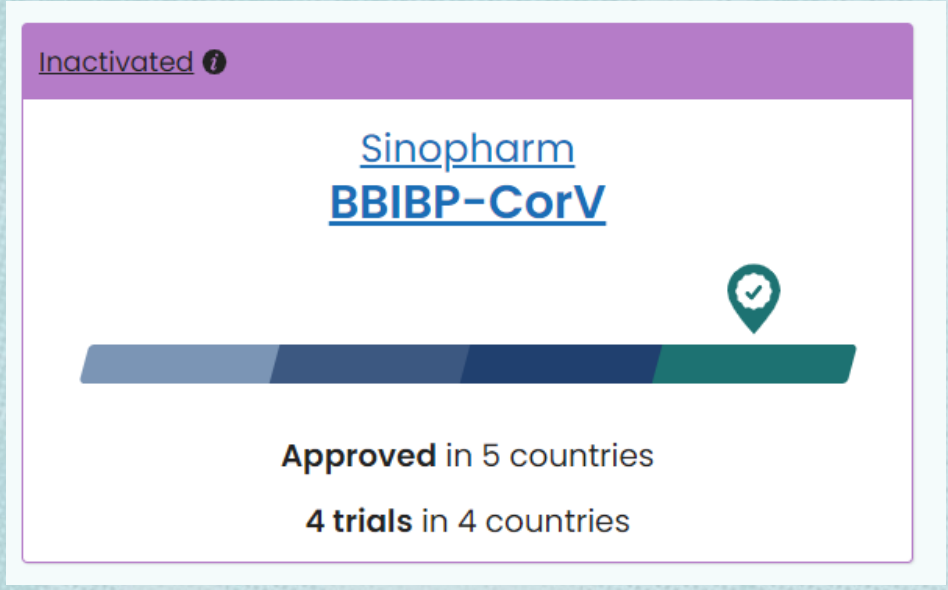


One dose vaccine

Results expected by the end of January

https://covid19.trackvaccines.org/

Status update



Almost a million people have been given an experimental Chinese coronavirus vaccine, pharmaceutical giant claims

By Ben Westcott and Sophie Jeong, CNN
Updated 11:03 AM ET, Fri November 20, 2020

https://covid19.trackvaccines.org/

NEXT STEPS

UF

What's ahead in Phase 3 COVID-19 vaccine trials

- More Phase 3 trial results to come…
- *What happens to ongoing/planned trials?*
- Important that there is a clear pathway for generating evidence to support full licensure
- Do not discount the "tortoises"

UF

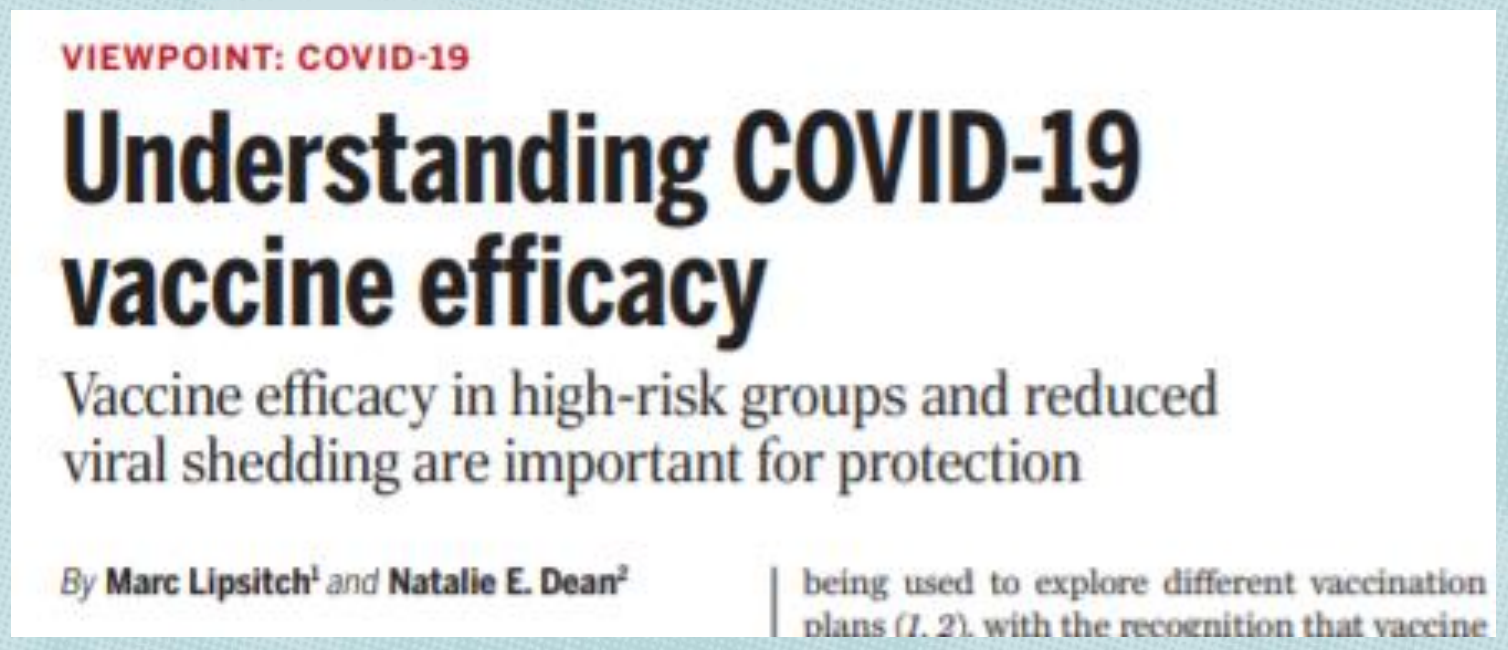
Planning future trials amidst uncertain epidemiology

- Flexible trial design that uses a master or core protocol
- Modeling provides a data-driven approach for trial planning, site selection, feasibility assessment
- To come…
  - Correlates analysis
  - Observational studies

Dean et al. 2020 New England Journal of Medicine DOI: 10.1056/NEJMsb1905390
Dean et al. 2020 Vaccine https://www.sciencedirect.com/science/article/pii/S0264410X20311919?via%3Dihub

Key Open Questions

- ❑ Long-term efficacy/safety
- ❑ Subgroup specific effects
- ❑ Ability of the vaccines to prevent infection or otherwise reduce infectiousness



VIEWPOINT: COVID-19

Understanding COVID-19 vaccine efficacy

Vaccine efficacy in high-risk groups and reduced viral shedding are important for protection

By **Marc Lipsitch**[1] *and* **Natalie E. Dean**[2]

being used to explore different vaccination plans (*1*, *2*), with the recognition that vaccine

Science 2020, DOI: 10.1126/science.abe5938

CONCLUSION

Conclusion

- COVID-19 vaccine trials present a new paradigm for vaccine evaluation
- Because of widespread community transmission, these trials have been able to rapidly generate evidence
- It is critical that there remains a pathway for evaluating other vaccines, as we want diverse and widely available products to meet global need

THANK YOU!

Natalie Dean
nataliedean@ufl.edu

This work is supported by
NIH/NIAID R01-AI139761