Some Considerations on Developing COVID-19 Vaccines

Bo Fu, Ya Meng, Josh Chen

Sanofi Pasteur, Swiftwater, PA

National Institute of Statistical Science (NISS) and Merck Workshop

September 16, 2020

Disclaimer

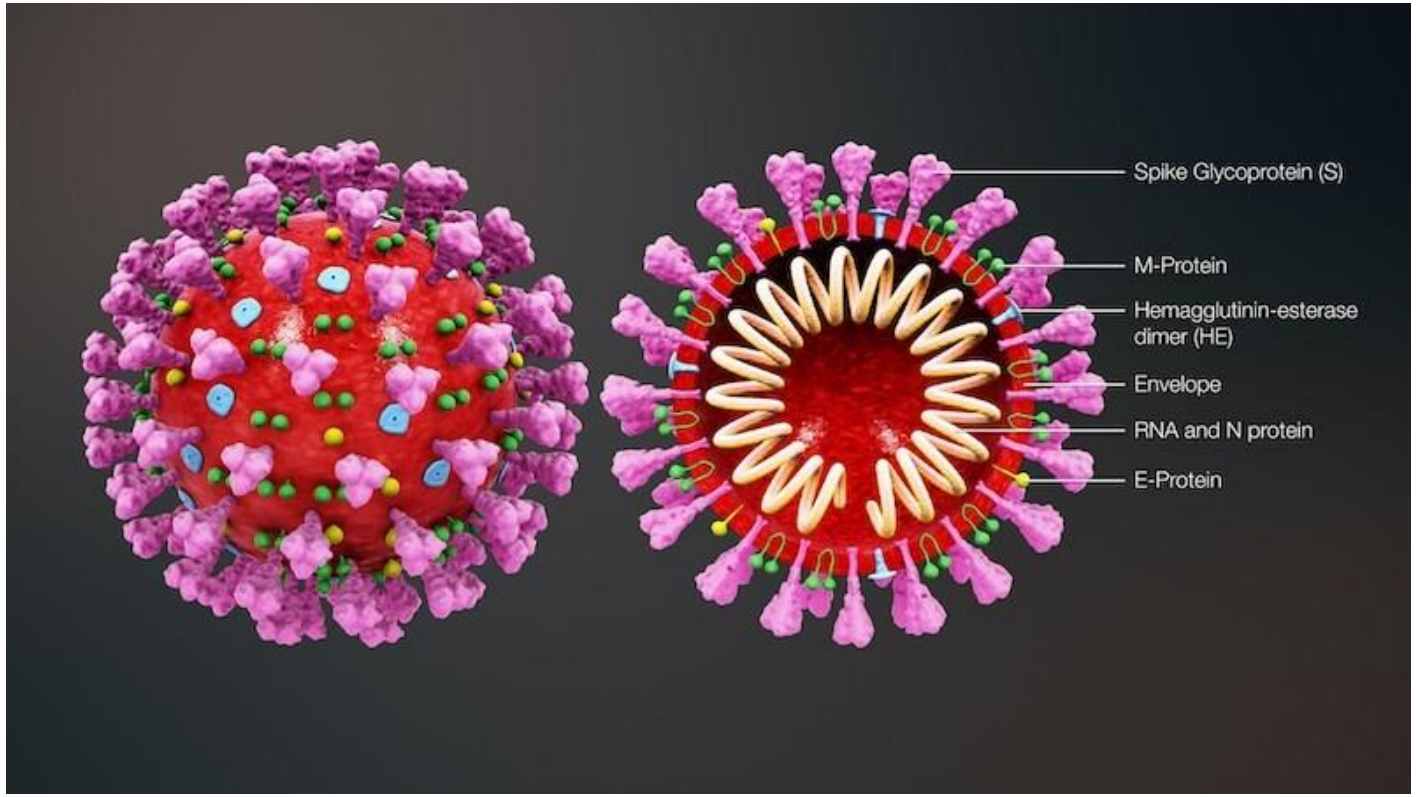
The views expressed in this presentation are those of the speakers, and do not necessarily reflect the views of their employer

Information in this presentation is available in public domain

Topics

- The science
- Regulatory pathway
- Clinical plan and design considerations

Coronaviruses and the novel SARS-CoV-2 that causes COVID-19



http://sdcity.edu/about/communications/covid19/

Common human coronaviruses
(account for 15 to 30% of common colds)*

- 229E (alpha coronavirus)
- NL63 (alpha coronavirus)
- OC43 (beta coronavirus)
- HKU1 (beta coronavirus)

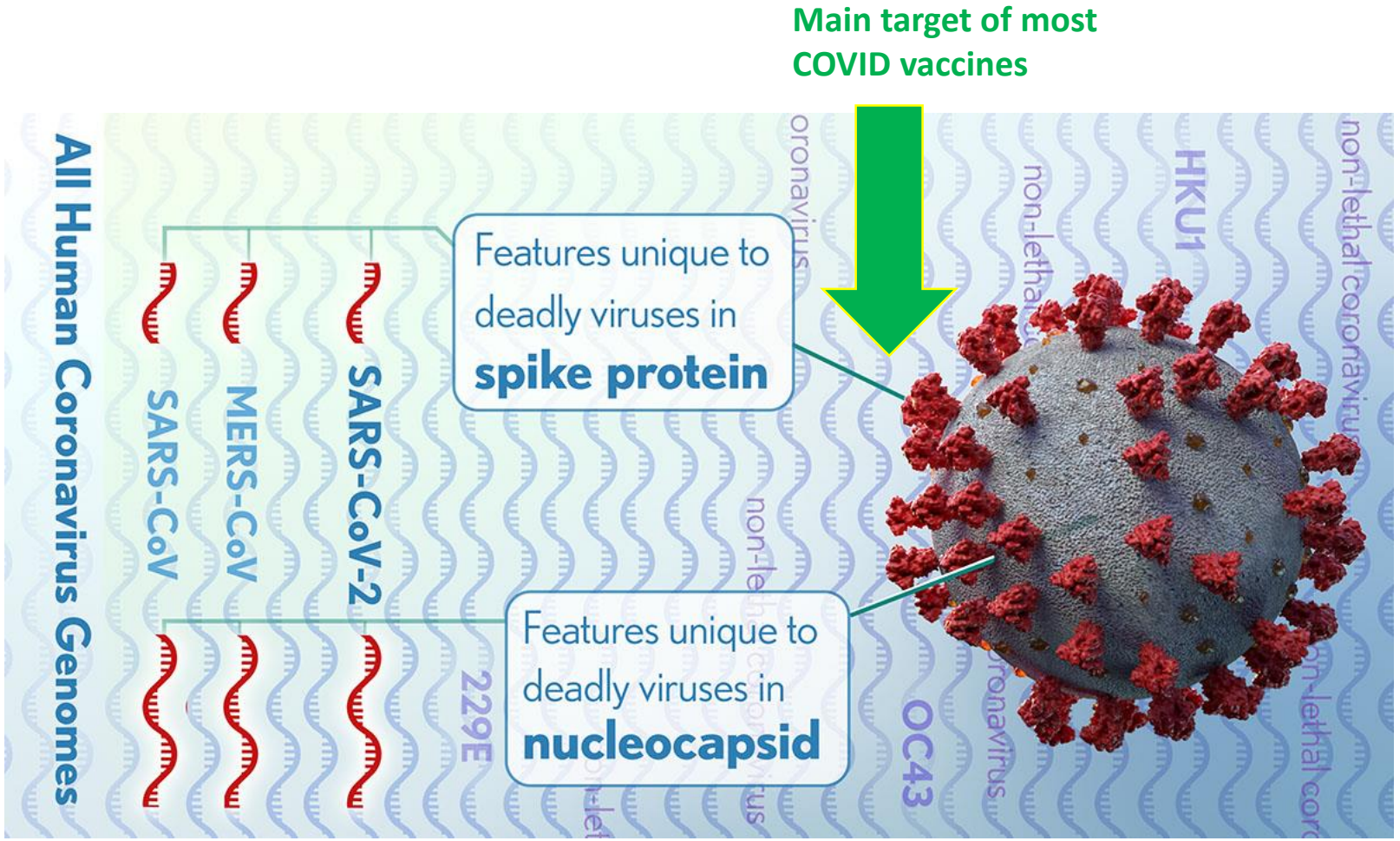
Other human coronaviruses

- MERS-CoV
- SARS-CoV
- SARS-CoV-2 (novel coronavirus causing COVID-19)

https://www.cdc.gov/coronavirus/types.html

* Mesel-Lemoine et al, J Virol. 2012; 86: 7577–7587

SARS-CoV-2: key genomic differences from other coronaviruses that cause less severe disease

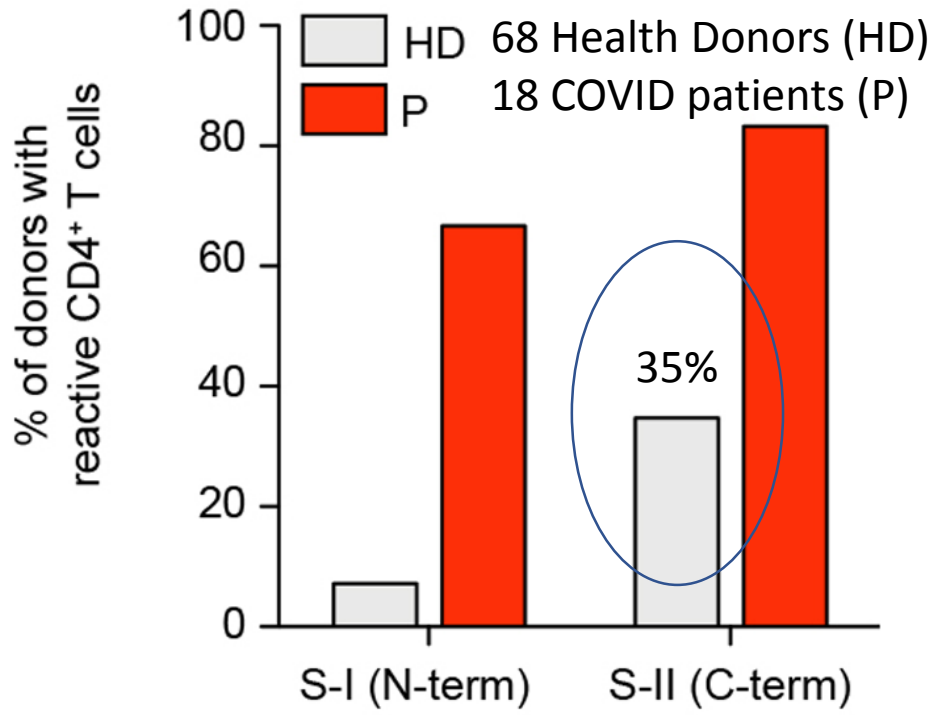


Regions (red) that might code for lethal differences in the virus that causes COVID-19 as well as SARS and MERS.

These differences could be targets for testing or treatments.

Gussow et al, PNAS June 30, 2020 117 (26) 15193-15199

Could prior exposure to common cold coronaviruses provide cross-protection for severe COVID-19?



- Isolated immune cells stimulated by segment of SARS-CoV-2 'spike proteins'
  - Overlap between common cold coronaviruses and SARS-CoV-2: C-terminal domain > N-term
- Results
  - As expected, high 85% (15/18) of patients had re-activated CD4+ T cells to C-term
  - Surprisingly, 35% (24/68) healthy individuals also activated to SARS-CoV-2 C-term
- Implications for the design and analysis of upcoming COVID-19 vaccine trials?

Braun, J., Loyal, L., Frentsch, M. *et al.* SARS-CoV-2-reactive T cells in healthy donors and patients with COVID-19. *Nature* (2020). https://doi.org/10.1038/s41586-020-2598-9

Table 1. Categories of vaccines for protection against SARS-CoV-2 infection and/or disease [1]

Vaccine category	Safety[2]	Speed and ease of production	Logistics of global distribution	Potential for NAb induction	Potential for cell-mediated immunity[3]
Live attenuated virus	Substantial concerns	N/A[4]	N/A	Probably high	Probably Good
Inactivated virus	Some concerns[5]	Intermediate	Feasible	Moderate	Poor
✓ Non-replicating virus vector (recombinant DNA virus)	High	High	Feasible	Weak	Probably good
DNA plasmid given by electroporation	High	High	Some concerns[6]	Very weak	Probably good
✓ mRNA	High	High	May be difficult[7]	Weak	Probably good
✓ Soluble or nanoparticle S- or RBD-protein, with adjuvant	High	Low[8]	Feasible	High	Poor

1 full list on WHO website.

2 Safety indicates the likelihood the vaccine will be tolerated without serious adverse effects in the absence of infection.

3 Most emphasis has been placed on the induction of NAbs, although some data on cellular immune responses are emerging from animal studies and more will be obtained in human trials.

4 N/A, not applicable. There are no known plans to produce this type of vaccine.

5 For a killed virus vaccine to be safe, the pathogen must be fully inactivated. Historically, inactivation has sometimes been incomplete (e.g., with polio vaccines).

6 Delivering DNA vaccines into muscles via electroporation is a relatively complex procedure compared to direct injection via needles or oral delivery.

7 The ease with which mRNA vaccines can be formulated and distributed has not been widely discussed. However, if these vaccines turn out to be unstable at ambient temperatures it will be challenging to distribute frozen or chilled stocks.

8 General experience suggests that producing a stable cell line and using it to make large stocks of recombinant proteins under Good Manufacturing Process conditions can take 1-2 years.

✓ clinical data available (Aug, 2020)

John P. Moore and P. J. Klasse. SARS-CoV-2 vaccines: 'Warp Speed' needs mind melds not warped minds. J. Virol. doi:10.1128/JVI.01083-20, Posted Online 26 June 2020

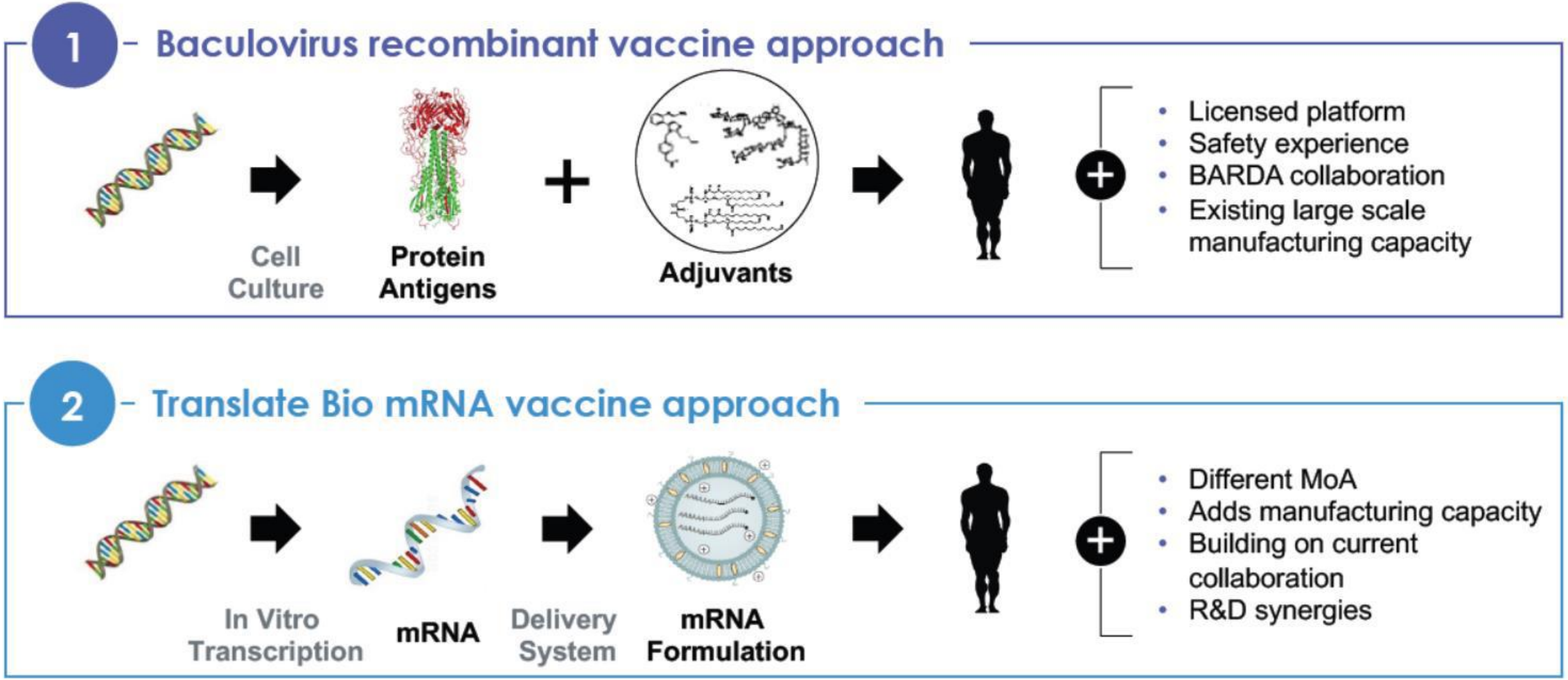
Current COVID-19 Vaccine Candidates

Vaccine Technique	Vaccine Candidate Company	2020				2021			
		Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4
mRNA	Moderna		Ph1	Ph2	Ph3				
	Pfizer/BioNTech		Ph1/2	Ph2b/3					
Protein based	Novavax		Ph1/2						
	Sanofi Pasteur				Ph1/2	Ph3			
Viral vector	AstraZeneca/Oxford		Ph1	Ph2	Ph3				
	Cansino		Ph1	Ph2	Ph3				
	Merck/Themis				Ph1				
	Janssen			Ph1/2	Ph3				

Latest update: August 10, 2020

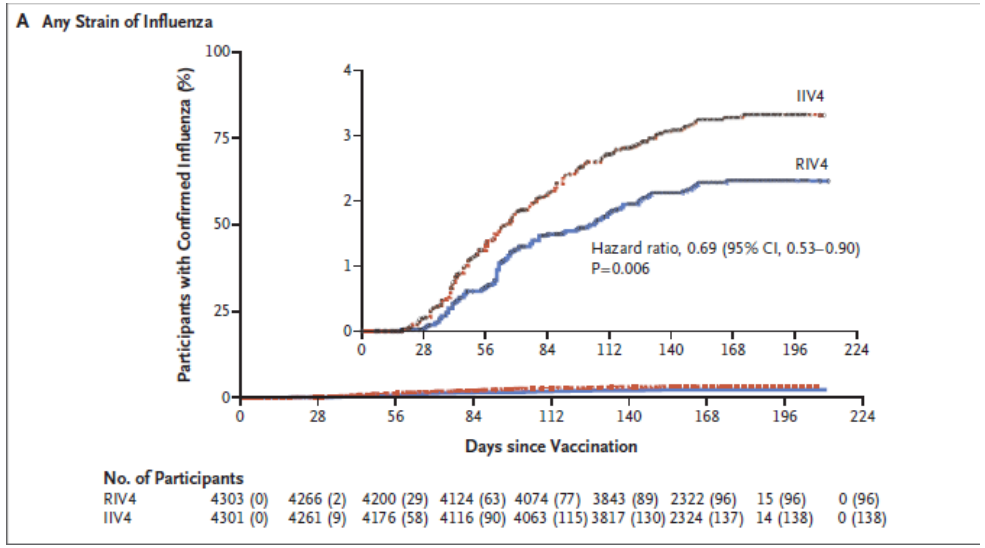
SANOFI

Sanofi Pasteur: two approaches for COVID vaccines



Protein based, Baculovirus recombinant platform established and well-understood

Licensed vaccine against flu



Dunkel et al. N Engl J Med 2017;376:2427-36.

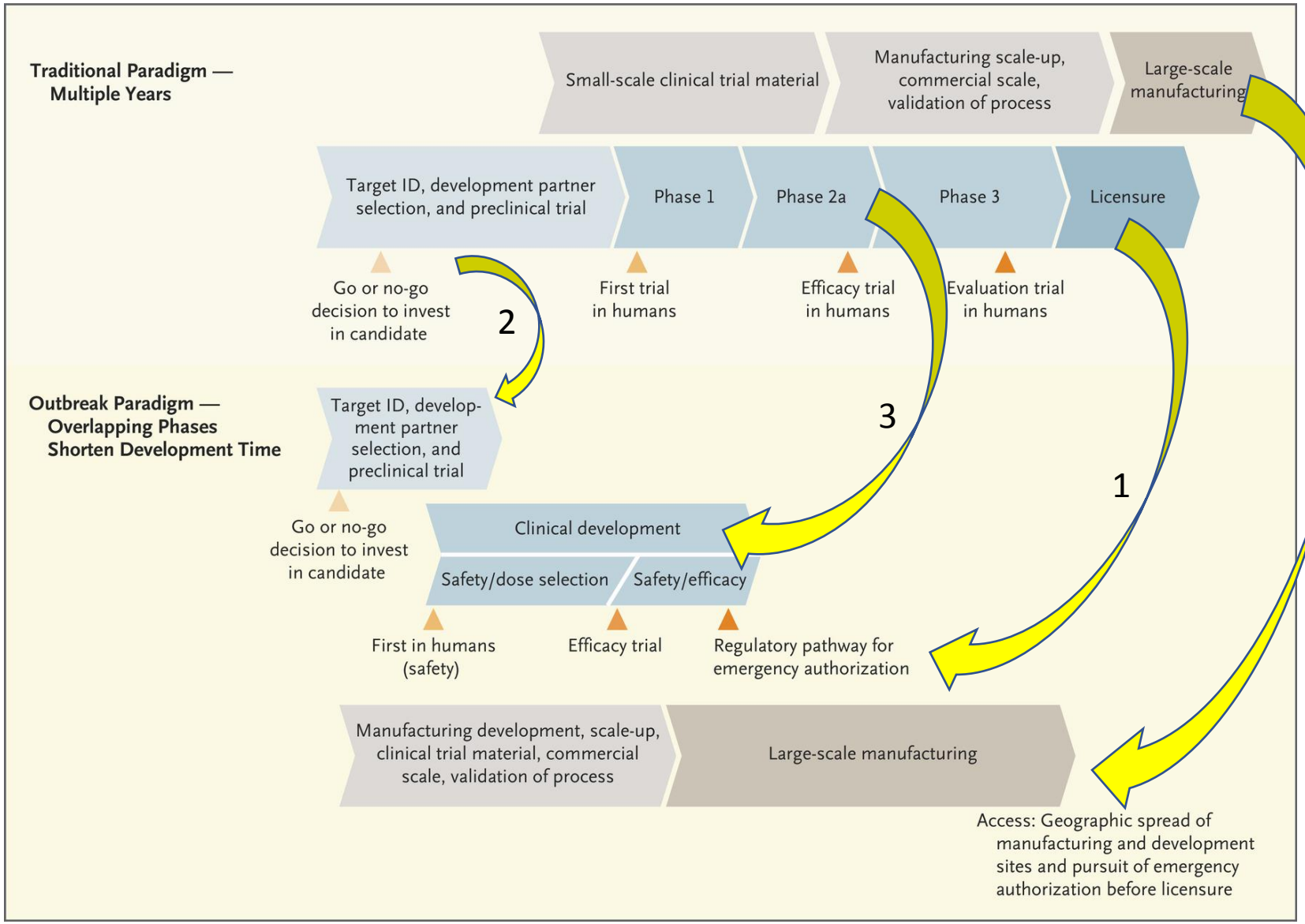
Early work in SARS

Available online at www.sciencedirect.com
SCIENCE DIRECT®
Vaccine 24 (2006) 3624–3631
Vaccine
www.elsevier.com/locate/vaccine

A recombinant baculovirus-expressed S glycoprotein vaccine elicits high titers of SARS-associated coronavirus (SARS-CoV) neutralizing antibodies in mice

Zhimin Zhou[a,*], Penny Post[a], Rick Chubet[a], Katherine Holtz[a], Clifton McPherson[a], Martin Petric[b], Manon Cox[a]

Traditional vs Pandemic Paradigm
Challenges and Opportunities for Vaccine Development

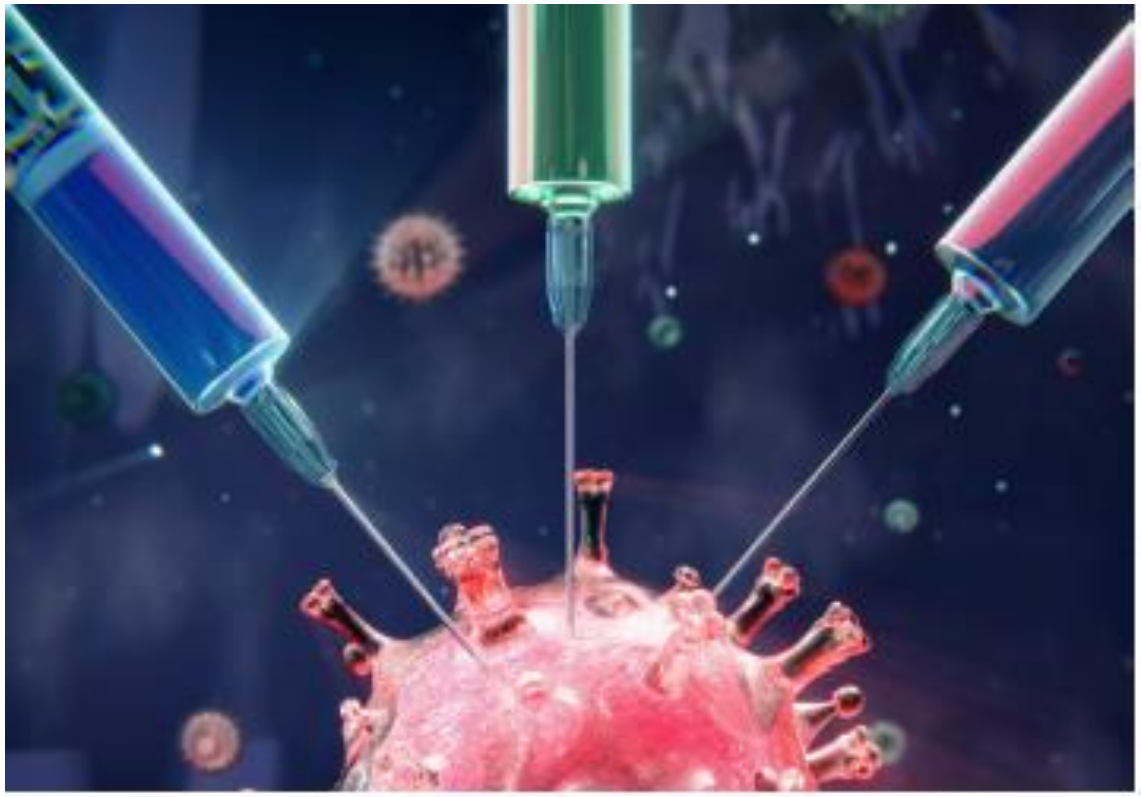


Opportunities for pandemics

1. **Accelerated regulatory pathway**
2. **Shortened discovery and pre-clinical**
3. **Streamlined clinical development**
4. **At-risk manufacturing scale-up**

Adopted from: N Lurie et al. N EnglJ Med 2020. DOI: 10.1056/NEJMp2005630

“There is no accelerated pathway for COVID-19 or any other emerging infectious disease”



Credit: Phang GFX / Alamy Stock Photo

The pandemic pipeline

Companies are doing their best to accelerate experimental drugs and vaccines for COVID-19 through the pipeline. Each faces its own set of challenges, but all agree on the need for a radical rethink of the clinical development process for pandemics.

John Hodgson

Nature Biotechnology | VOL 38 | May 2020 | 523–532

Regulatory path options

FDA Guidance, June 2020
- **EUA+ (Emergency Use Authorization, plus), September 2020**

REUTERS

Sinovac's coronavirus vaccine candidate approved for emergency use in China – source

AUGUST 28, 2020. BEIJING (Reuters) - Sinovac Biotech Ltd's coronavirus vaccine candidate CoronaVac was approved for emergency use as part of a programme in China to vaccinate high-risk groups such as medical staff, a person familiar with the matter said.

abcNEWS

Russia's approval of virus vaccine greeted with some alarm

Russia has become the first country to approve a coronavirus vaccine for use among tens of thousands of its citizens

By VLADIMIR ISACHENKOV and DARIA LITVINOVA Associated Press
August 11, 2020, 9:27 AM • 6 min read

https://investors.modernatx.com/news-releases/news-release-details/moderna-highlights-opportunity-mrna-vaccines-its-first-vaccines

FDA guidance

Development and Licensure of Vaccines to Prevent COVID-19

Guidance for Industry

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research
June 2020

Key points:

- Traditional approval paradigm: efficacy demonstration required
  - no accepted surrogate
  - EUA possible
- Acceleration of pre-clinical safety evaluation for established platforms
- Use of adaptive and seamless designs
- Inclusion of diverse populations
- Randomized, placebo-controlled Ph3 efficacy trial
  - “COVID-19 disease” and “infection” endpoints
  - vaccine efficacy LB 30%, point estimate 50%+

PREVISIONPOLICY

September 11, 2020

COVID-19 Vaccines Likely Available Through "EUA-Plus" Pathway, FDA's Marks Says; More Guidance Coming On Emergency Use Standards

FDA is re-framing the likely regulatory pathway for the first vaccines against the SARS-CoV-2 virus as "Emergency Use Authorization-plus" — by which vaccines would meet a higher standard than a traditional EUA but would not check all the boxes required for a full Biologics Licence Application.

A typical combined Phase 1 / 2 study

- A small safety sentinel cohort (in 10s) followed by a larger dose ranging study (usually in 100s to allow Go/No-Go and dose selection for Phase 3)
- Dose formulations to be studied
  - Lower and upper range of dose level
  - 1- vs 2-injection
  - Adjuvant for antigen-sparing, due to limited manufacturing capacity
- Keep in mind: data rollout and criteria for faster & robust Go/No-Go decision and dose selection

Dose, Dose, Dose

- Biomarkers
  - binding and neutralizing antibody titers, and their relevance?
  - T cell responses and their role in fighting the virus?
- Use of adjuvant for antigen-sparing
  - For pandemic: 5µg/adju vs 25µg can “increase” manufacturing capacity by 5-fold
- Criteria
  - Maximum Tolerable Dose (MTD) – efficacy
  - Minimum Effective Dose (MED) – safety & capacity
  - Reference: convalescent samples – similar? 2-fold higher? 5-fold?
- Other considerations
  - At risk populations (likely early adopters): e.g. elderly, likely lower immune responses & safety concern

The Guardian

Immunity to Covid-19 could be lost in months, UK study suggests

Exclusive: King's College London team found steep drops in patients' antibody levels three months after infection

Coronavirus - latest updates
See all our coronavirus coverage

Ian Sample *Science editor*

Sun 12 Jul 2020 12.31 EDT

Push for higher titers than natural infection?

Humoral Immune Response to SARS-CoV-2 in Iceland. Gudbjartsson et al, September 1, 2020, NEJM.org. DOI: 10.1056/NEJMoa2026116.

> *Our results indicate that antiviral antibodies against SARS-CoV-2 did not decline within 4 months after diagnosis.*

Randomization Ratio: Equal vs Unequal?

Unequal ratio could increase the chance of observing imbalance in rare, serious safety events, with bias against larger arm

STATISTICS IN BIOPHARMACEUTICAL RESEARCH
2020, VOL. 12, NO. 3, 279–283
https://doi.org/10.1080/19466315.2019.1689846

Imbalanced Randomization in Vaccine Clinical Safety Trials

Scott Patterson[a], Fabrice Bailleux[b], Josh Chen[a], and Ming Zhu[a]

[a]Sanofi Pasteur, Swiftwater, PA, USA; [b]Sanofi Pasteur, Marcy L'Etolle, Lyon, France

Real Example: In a late phase trial, there were 10 cardiovascular events on vaccine and 1 on control. The randomization ratio was 3:1 (nv=1668 vaccine, and nc=554 on control).

Probability of observing risk ratio >3 for rare safety events (p=0.1% or 1%)

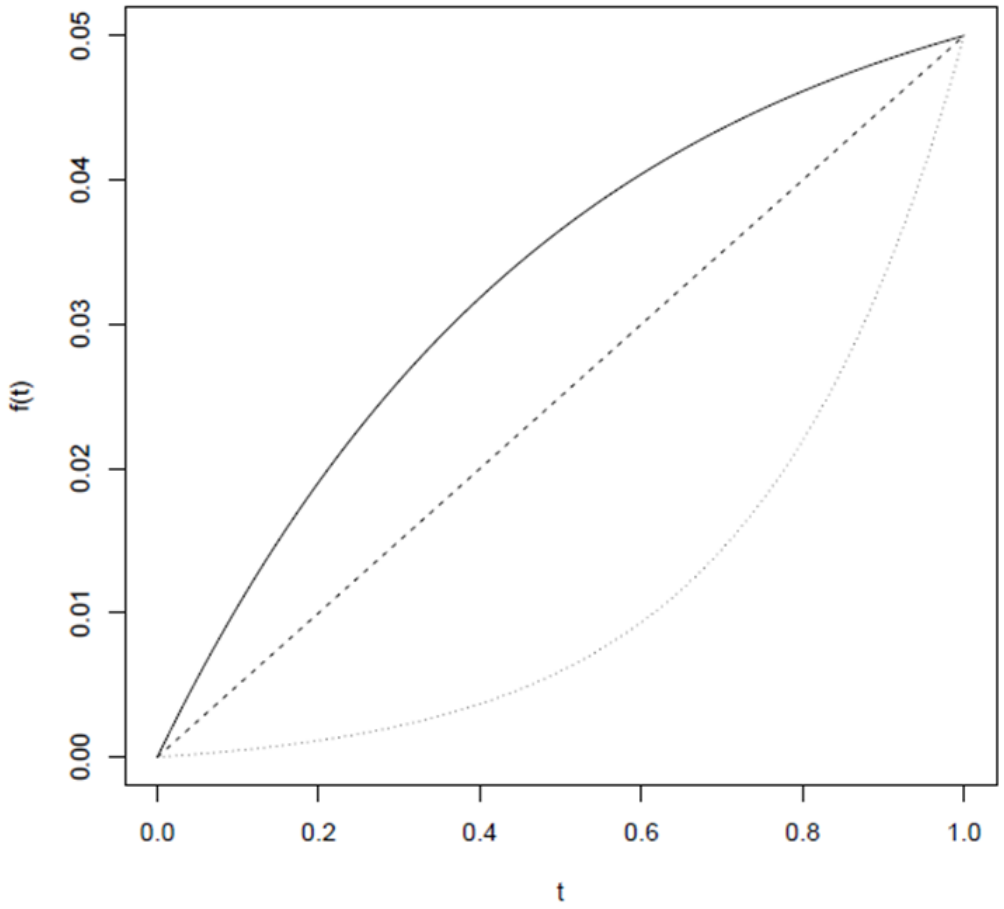
p	Probability $n_V = n_C = 1000$	Probability $n_V = 1500, n_C = 500$
0.001	0.059	0.116
0.01	0.017	0.060

Prob. include 0 events on control and ≥3 for vaccine.
Sample size nv and nc for vaccine and control, respectively

Diverse populations

- Inclusion of diverse populations recommended (or, required?)
  - At-risk populations (healthcare workers, comorbidities)
  - Demographics (age/elderly, racial and ethnic minorities, country, etc.)
  - Immuno-compromised populations (e.g., HIV)
  - Sero-negative and sero-positive populations
- However, expectation to demonstrate efficacy in each sub-population not realistic
  - Consistency, correlate of protection, biomarker extrapolation: opportunity for statistical contributions
- Also note possible differences in benefit/risk threshold for sub-populations
  - Children: lower risk, higher requirement for safety … well established platform?

Alpha-spending function for interim efficacy analysis: speed vs power



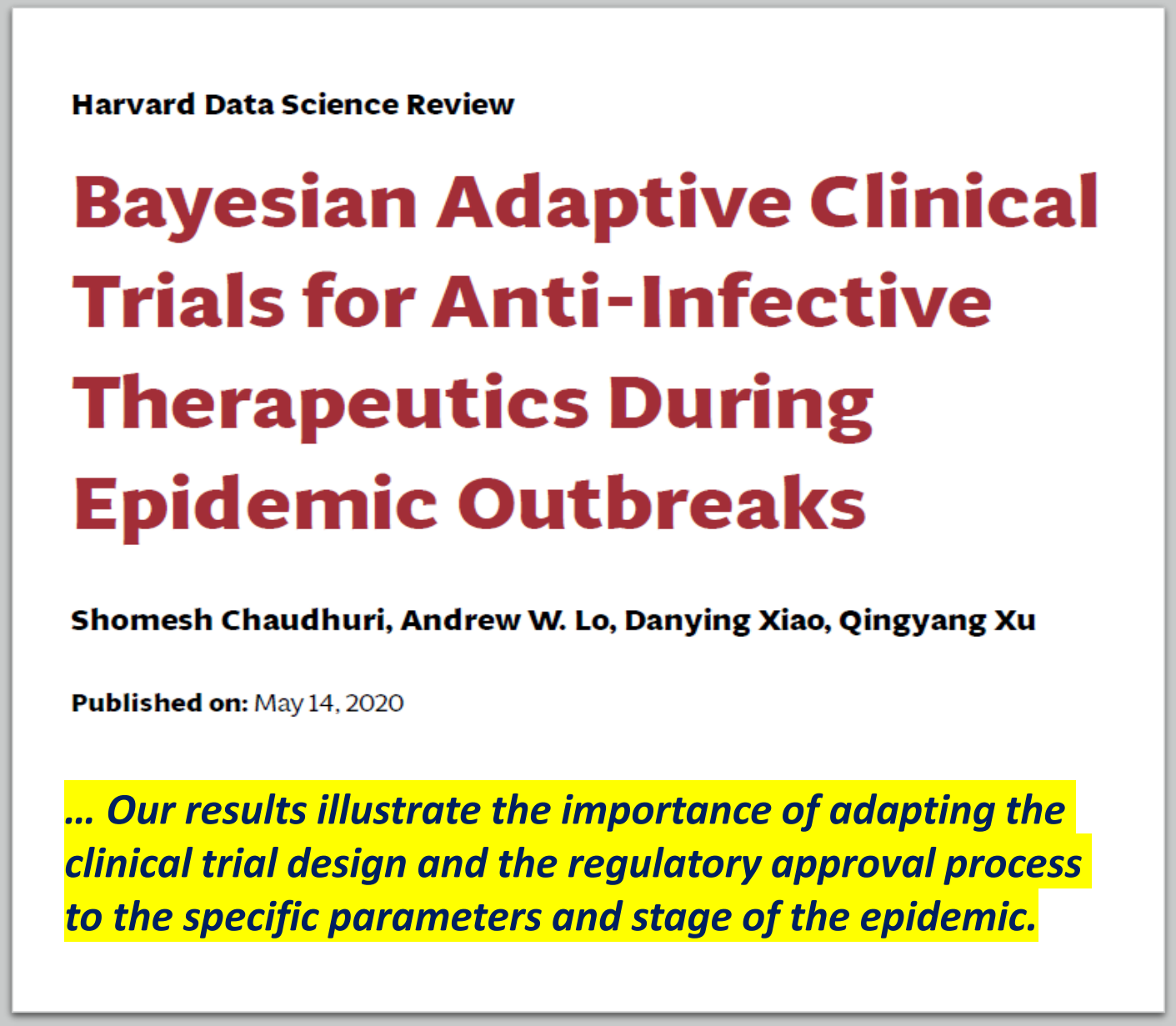
Pocock spending functions spends more alpha for early interim analyses

Linear spending?

O'Brien-Fleming spending function spends more for late analyses

Unchartered situation, requiring vigilance and adaptation

- What if case accrual not as fast as hoped?
- What if leading vaccines not highly effective as hoped?
- What if first approvals make it challenging to use placebo in subsequent trials?
- What if much worse "2nd wave" as happened during the 1918 flu pandemic?
- What if …



Harvard Data Science Review

Bayesian Adaptive Clinical Trials for Anti-Infective Therapeutics During Epidemic Outbreaks

Shomesh Chaudhuri, Andrew W. Lo, Danying Xiao, Qingyang Xu

Published on: May 14, 2020

… Our results illustrate the importance of adapting the clinical trial design and the regulatory approval process to the specific parameters and stage of the epidemic.

For example: what if slow case accrual?

- Manageable
  - Enrolling & running multiple Ph3 studies, each with 30K-60K healthy subjects
  - Sizable safety database
- **Unpredictable**
  - Accrual of COVID cases, for multiple studies
  - Pandemic landscape: when, where, who?

Where to find shrimp?
And be lucky 10 days in a row?

Alternative approaches for timely decisions?

Concluding remarks

- Our science about the novel SARS-CoV-2 virus and COVID-19 disease is evolving at daily basis
- Race against the virus to develop safe and effective vaccines needs consideration of both speed and risk
  - In this global pandemic, safety of the COVID vaccines is paramount for use in millions of otherwise healthy people
- Given the unique challenges in this global pandemic, one-size-fit-all vs “adaptive” approach as science & knowledge advance
- Opportunities for quantitative scientists to guide the development of COVID vaccines in this unchartered water