The Future of Vaccines: Securing the Promise

Julie Louise Gerberding, MD, MPH

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Conflicts of Interest

- Adjunct Associate Professor of Medicine (Infectious Diseases), University of California, San Francisco
- Adjunct Professor of Medicine (Infectious Diseases), Case Western Reserve University
- Trustee, Mayo Clinic
- Trustee, Case Western Reserve University
- Co-Chair, CSIS Commission on Strengthening America's Health Security
- Board Director, National Health Council
- Board Director, HilleVax
- Board Director, Summerbio
- Board Director, AfterNext HealthTech

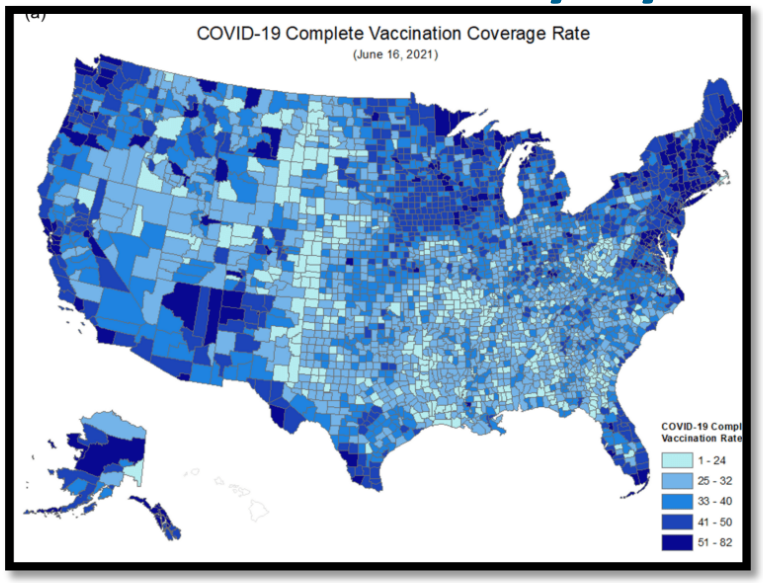
Objectives

- Describe an end-to-end framework for optimizing vaccine impact
- Define critical opportunities for innovation to solve vexing vaccine challenges
- Inspire assertive strategies to build confidence in current and future vaccination recommendations and to combat mis/disinformation

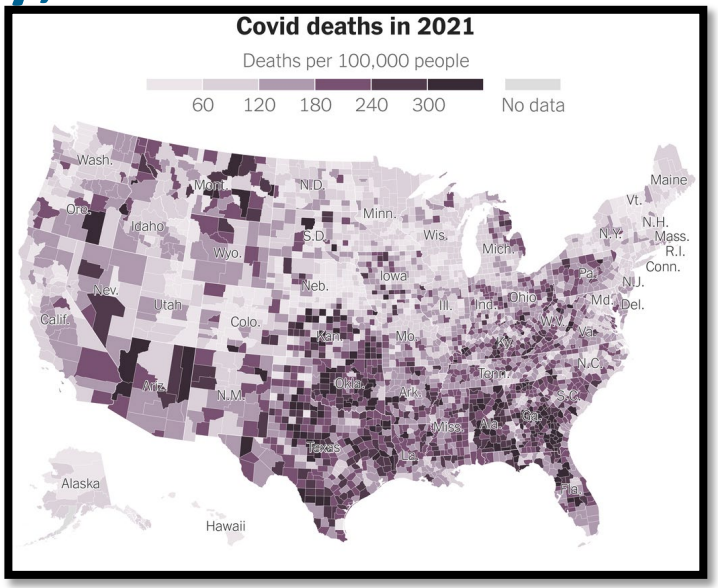
SARS-CoV-2 Vaccination: Some Lessons Learned

1. Science is on our side
2. Good science takes time - and evolves over time
3. Faster was not really fast enough
4. We need “advanced generation” vaccines
5. Equitable vaccine access remains elusive
6. Trust is the biggest challenge

U.S. Vaccine Equity: SARS-CoV-2 Vaccination and COVID-19 Mortality by County, 2021



Data as of June 2021
John's Hopkins University Center for Systems Science and Engineering
https://systems.jhu.edu/research/public-health/covid-19-vaccine/ Accessed 01/2023



Data as of November 2021
Source: New York Times database; reported by David Leonhardt
https://www.google.com/search?rlz=1C9BKJA_enUS1007US1008&hl=en-US&q=covid+deaths+us+2021+map&tbm=isch&sa=X&ved=2ahUKEwiVwcORtcD8AhVUI0QIHauDAIQ0pQJegQICRAB&biw=935&bih=560&dpr=2#imgrc=4cxIsoat707Bnaccessed 01/2023

U.S. Vaccine Equity: Risk of SARS-CoV-2 Infection, Hospitalization, and Death by Race/Ethnicity

Rate ratios compared to White, Non-Hispanic persons	American Indian or Alaska Native, Non-Hispanic persons	Asian, Non-Hispanic persons	Black or African American, Non-Hispanic persons	Hispanic or Latino persons
Cases[1]	1.5x	0.8x	1.1x	1.5x
Hospitalization[2]	2.5x	0.7x	2.1x	1.9x
Death[3, 4]	2.1x	0.8x	1.6x	1.7x

CDC updated 12/2022; accessed 01/2023
https://www.cdc.gov/coronavirus/2019-ncov/covid-data/investigations-discovery/hospitalization-death-by-race-ethnicity.html#print

[1]Data Source: Case level surveillance data from state, local and territorial public health jurisdictions (data through December 7, 2022). Numbers are ratios of age-adjusted rates standardized to the 2019 U.S. intercensal population estimate. Calculations use only the 65% of case reports that have race and ethnicity; this can result in inaccurate estimates of the relative risk among groups.

[2] Data source: COVID-NET (March 1, 2020, through December 3, 2022). Numbers are ratios of age-adjusted rates standardized to the 2020 US standard COVID-NET catchment population.

[3] Data Source: National Center for Health Statistics Provisional Death Counts (data through December 3, 2022). Numbers are ratios of age-adjusted rates standardized to the 2019 U.S. intercensal population estimate.

End-to-End ACCESS to Health Protection

- ACTUALIZATION: new vaccine solutions are created in a supportive innovation ecosystem
- APPROVAL: safe and effective products earn regulatory approval
- AVAILABILITY: global vaccine supply is equitable and reliable
- AFFORDABILITY: procurement and payment systems work
- ADVOCACY: evidence-based guidelines and policies promote proper use
- ACCESSIBILITY: vaccination services are convenient
- ACCEPTABILITY: people accept vaccination and are confident in its value

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Vaccine actualization is not for the faint-hearted!

ACTUALIZATION: Creating New Vaccine Solutions

What Needs to Be True?

- ✓Innovators: passionate research and development scientists with new ideas who are not afraid to fail
- ✓Investors (government, private sector, non-profits, and philanthropists) willing to put substantial capital at risk
- ✓Innovation ecosystem that motivates sustained commitment and reward
- ✓BREAKTHROUGHS!

Future Outlook: HIV Vaccine

Global pandemic continues…

- ✓1.5 M new infections each year
- ✓38 million people are living with HIV including 1.7 million children
- ✓Despite life-saving antiretroviral treatment, progress may be slowing and inequities are growing
- ✓An effective vaccine is necessary to end the pandemic

Vaccine track record…

- ✓8 completed vaccines trials since HIV was discovered in 1983
- ✓Both B-cell and T-cell immunogens and many platforms have been tried
- ✓Only one trial demonstrated efficacy – but only 31% - too low for further development
- ✓One big challenge is HIV strain variability

The Idea: Vaccinate to Elicit Broadly Neutralizing Antibodies (bNAbs) in Uninfected People

The Rationale

- ✓People with long-standing HIV infection may produce bNAbs that neutralize many HIV variants at once
- ✓Stimulating these bNAbs could form the basis of a cross-protective vaccine (or treatment) to get around the high variability of HIV strains
- ✓But the naïve B-cells that produce bNAbs are very rare and hard to stimulate with conventional vaccine antigens; they need to be coaxed into evolving higher affinity for a broader variety of virus strains
- ✓This will likely require priming and multiple boosts with antigen constructs that progressively broaden the immune response to HIV variants

The Excitement: First-in-Human Test of a Step Toward Inducing bNAbs in Uninfected People

- ✓A synthetic protein derivative called eOD-GT8, based on a part of the HIV envelope, was formulated as a nanoparticle candidate for bNAb priming of naïve B cells in germinal centers
- ✓In a small randomized double-blinded placebo-controlled study, healthy people were vaccinated with adjuvanted eOD-GT8 at baseline and 8 weeks
- ✓The desired bNAb precursors were induced in 97% of vaccine recipients; the precursors gained affinity and the expected somatic hypermutation profile
- ✓Establishes proof-of-concept for germline targeted vaccine priming and development of further boosting to achieve high affinity bNAbs against HIV

Leggat DJ, Cohen KW, Willis JR, et al. Vaccination induces HIV broadly neutralizing antibody precursors in humans. *Science*. 2022;378(6623):eadd6502. doi:10.1126/science.add6502

Future Outlook: "Universal" Coronavirus Vaccine

Coronavirus Threats

- ✓SARS-CoV-2 continues to evolve, spillover, and even spillback
- ✓Worrisome reports of emerging antiviral resistance
- ✓Three serious transmissible coronavirus outbreaks (SARS-CoV, MERS, and SARS-CoV-2) in just 2 decades
- ✓Coronaviruses are ssRNA viruses and many are hypervariable (as we have learned in the current pandemic)

"One Health" Pathogen

- ✓1930s, recognized threat to livestock, companion animals, and wildlife; 1960s, recognized URI threat to humans
- ✓Spillover from one species to another (including humans) is likely to continue (accelerate)
- ✓Betacoronavirus family poses the greatest threat to humans (so far) though alphacoronaviruses also cause mild to moderate URIs
- ✓One Health surveillance is inadequate at best

The Idea: Create a Broadly Protective Pan-Protective Coronavirus Vaccine

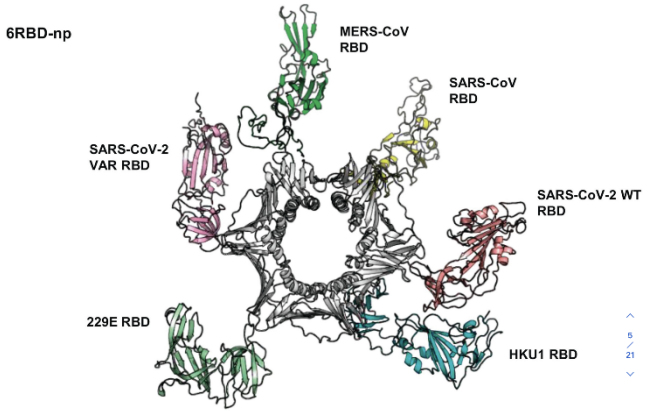
- ✓Protect against known and future emerging coronaviruses
- ✓Protect against variants as they emerge
- ✓Provide durable protection
- ✓"Holy grail" – unsuccessful quest for universal influenza vaccine despite decades of effort
- ✓Must meet many other criteria – affordable, low barriers to manufacturing, stability
- ✓CEPI focus: $230 million invested to date

One Strategy: Mosaic Antigens

✓Construct a stable protein scaffold

✓Attach antigenic peptides from coronavirus receptor binding domains (RBDs) from a variety of coronaviruses to the scaffold

✓Vaccinate with the mosaic vaccine



The Excitement: Mouse Model of a Mosaic Coronavirus Immunogen

- 6 different receptor-binding domains (RBDs) derived from α- and β-CoV were linked to proliferating cell nuclear antigen heterotrimeric scaffolds
- This mosaic multivalent nanoparticle, 6RBD-np, was used to immunize human angiotensin-converting enzyme 2–transgenic mice
- High antibody responses against RBD antigens derived from the α- and β-CoV and full protection against the SARS-CoV-2 challenges. This study provides proof of concept that the mosaic 6RBD-np
- Induced 100% protection against SARS-CoV-2 challenges with the potential to induce cross-reactivity

Lee DB, Kim H, Jeong JH, et al. Mosaic RBD nanoparticles induce intergenus cross-reactive antibodies and protect against SARS-CoV-2 challenge. *Proc Natl Acad Sci U S A*. 2023;120(4):e2208425120. doi:10.1073/pnas.2208425120

Acceptability: Restoring Confidence in Vaccine Information and Advice

- Crisis in trust
- Politicalization
- Infodemics
- Information overload
- Deadly for many

"Falsehood flies, and truth comes limping after it, so that when men come to be undeceived, it is too late; the jest is over, and the tale hath had its effect."

— Jonathan Swift

(The Examiner, no. XIV,Thursday, 9 November 1710)

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Myth: More Information Will Result in a Desired Belief or Action

People are bombarded with information.

Logical analysis of new information is unusual and almost impossible.

Mental shortcuts based on values, beliefs, and feelings are used to process most new information.

Information congruent with values and prior beliefs is accepted and incongruent information is ignored. In fact, more information may paradoxically encourage further polarization.

Myth: Improved interpretive skills alone will improve information processing and good decisions

Improving critical analysis, health literacy, and numeracy do help, especially in school-aged children.

But information processing is also social:

Our default is to trust what we hear and take it at face value unless:

- the information is obviously implausible
- the source is unlikeable or obviously untrustworthy
- we apply a lot of mental energy for a critique

Misinformation Flies!

Twitter falsehoods move faster, further, deeper, and broader across all categories, especially politics, than true stories

Falsehoods are usually novel and arouse negative emotions – anger, fear, disgust

Motivations to spread falsehoods:

- gossip and false narratives that frighten or anger people
- vested interests (industries, governments, etc.)
- "newsertainment" and false balance in the media
- lack of editorial "gatekeeping"
- social media algorithms to drive advertising revenue

People retain stories much longer than data!

Percent of Americans Who Trust National Spokespersons October 28, 2001

	% Who Would Trust
CDC Director (Dr. Koplan)	48%
Surgeon General (Dr. Satcher)	44%
AMA President (Dr. Corlin)	42%
HHS Secretary (T. Thompson)	38%
Homeland Security Secretary (T. Ridge)	33%
FBI Director (R. Mueller)	33%

R. Blendon, Harvard Program on Public Opinion and Health and Social Policy
International Communications Research of Media, PA

Percent of Americans Who Trust Local Spokespersons October 28, 2001

	% Who Would Trust
Personal doctor	77%
Fire department official	61%
Police department official	53%
Local hospital official	52%
State governor	48%
Local religious leader	46%

R. Blendon, Harvard Program on Public Opinion and Health and Social Policy
International Communications Research of Media, PA

Use the Trust You've Earned to Engage Others in Infectious Diseases Prevention and Control

- ✓Engage and inform your own networks of colleagues, family and friends
- ✓Correct misinformation and speak out against deliberate disinformation
- ✓Serve as a community expert resource via blogs, radio spots, podcasts, social media, op-eds, etc.
- ✓Advocate for evidence-based recommendations (e.g., vaccination)
- ✓Participate in community preparedness planning and exercising

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THANK YOU!