Update on COVID-19 Vaccines

Anthony S. Fauci, M.D.

Director

National Institute of Allergy and Infectious Diseases

National Institutes of Health

June 10, 2021

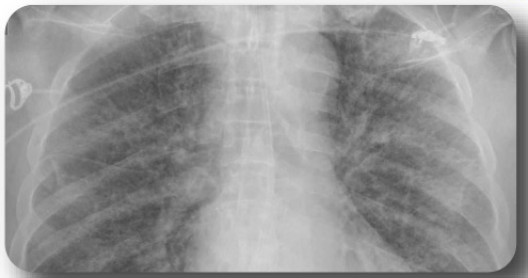
National Institute of Allergy and Infectious Diseases

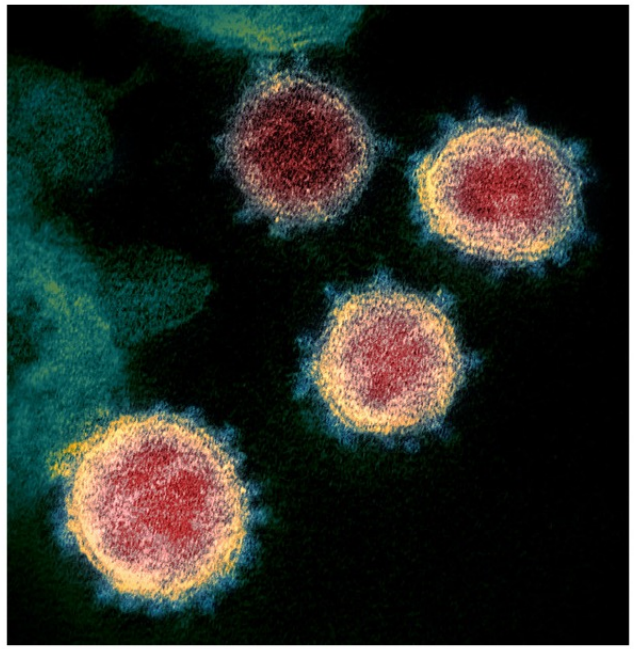
NIH Research on Coronavirus Disease 2019 (COVID-19)

Therapeutics

Diagnostics

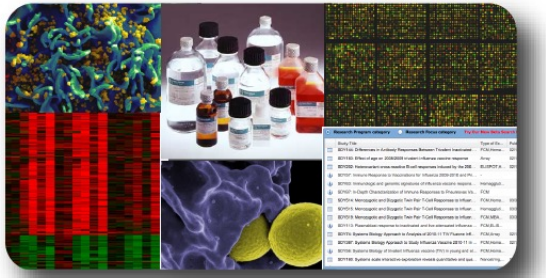
Natural History





Vaccines

Research Resources



Basic Research

NIH Research on Coronavirus Disease 2019 (COVID-19)

Therapeutics

Vaccines

Diagnostics

Research Resources

Natural History

Basic Research

April 9, 2021
Vol. 372, Issue 6538
Science

The Story Behind COVID-19 Vaccines

Anthony S. Fauci

"The speed and efficiency with which these highly efficacious vaccines were developed and their potential for saving millions of lives are due to an extraordinary multidisciplinary effort involving basic, preclinical, and clinical science that had been under way—out of the spotlight—for decades before the unfolding of the COVID-19 pandemic."

Role of NIH in the Development of COVID-19 Vaccines

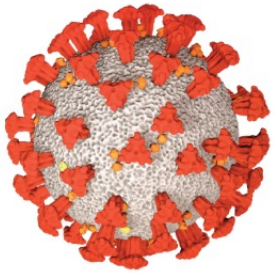
- Basic, pre-clinical, and clinical research to develop vaccine platforms

VRC Principal Investigators and Program Heads

Basic Research → Clinical Trials

- Stabilization of pre-fusion spike protein

- Extensive NIAID domestic and international clinical trials networks for HIV and influenza



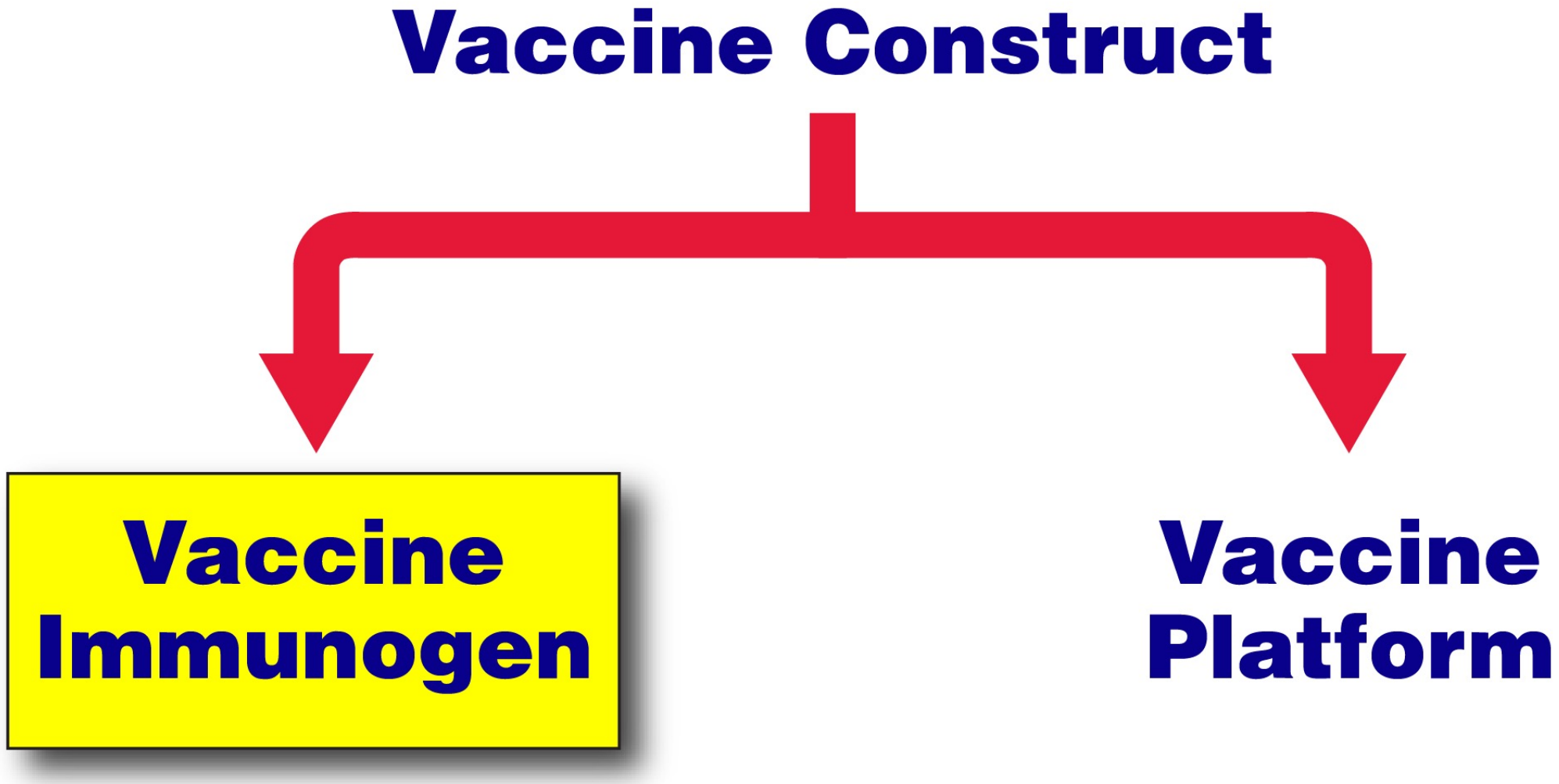
COVID-19 Prevention Network

Vaccine Construct

Vaccine Construct

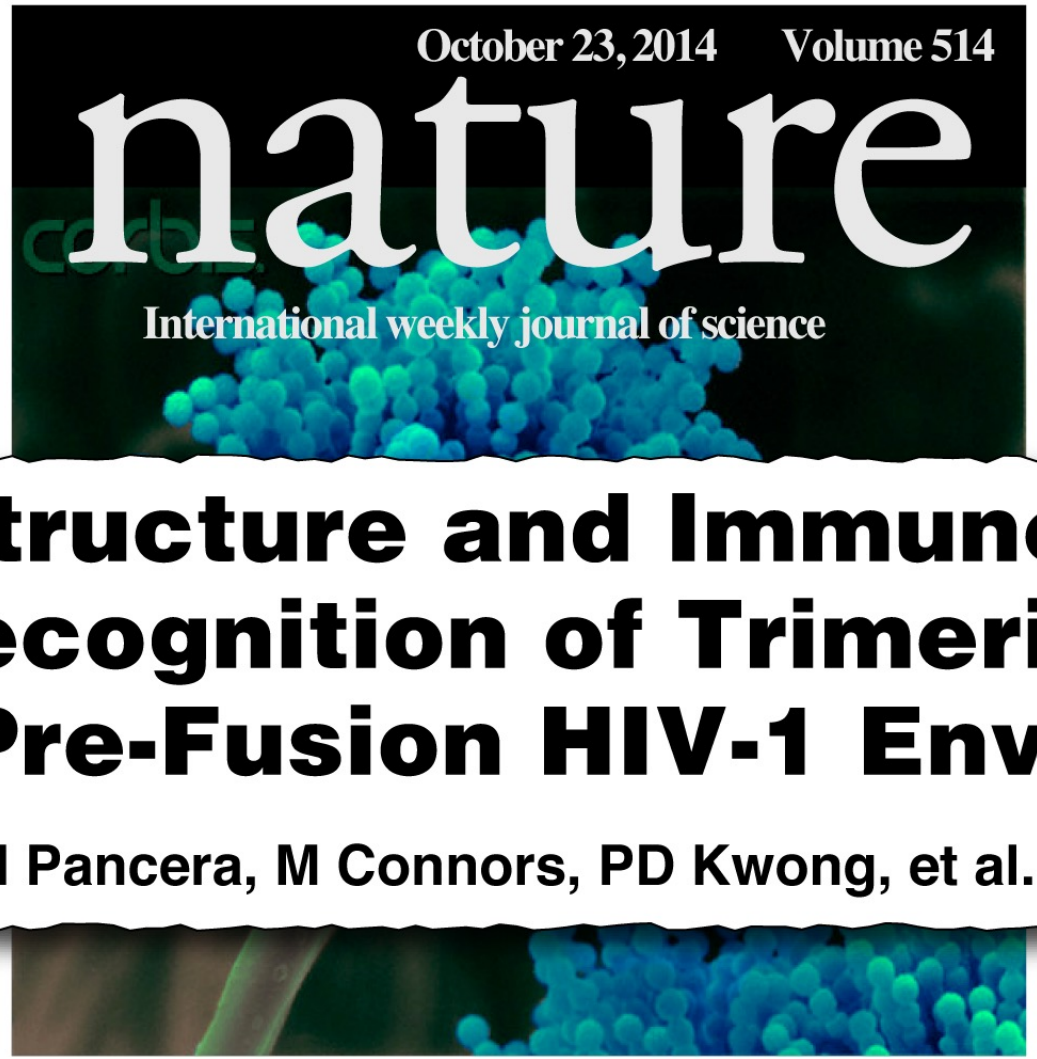
Vaccine Immunogen

Vaccine Platform


Vaccine Construct
Vaccine Immunogen
Vaccine Platform

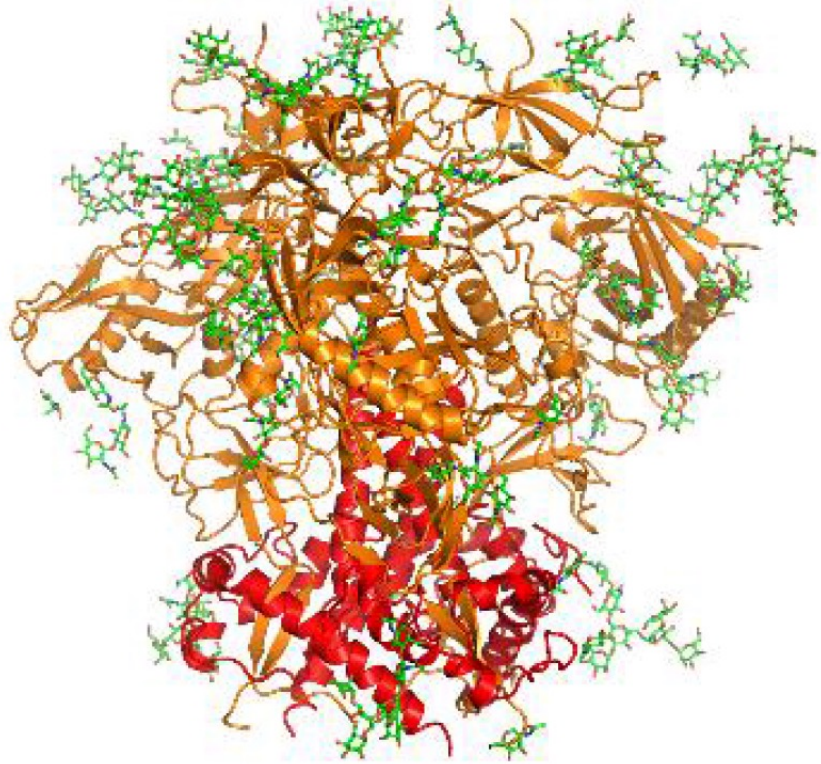
Structure-Based Vaccine Design

Stable, Soluble Structure of HIV Envelope Trimer



Structure and Immune Recognition of Trimeric Pre-Fusion HIV-1 Env

M Pancera, M Connors, PD Kwong, et al.

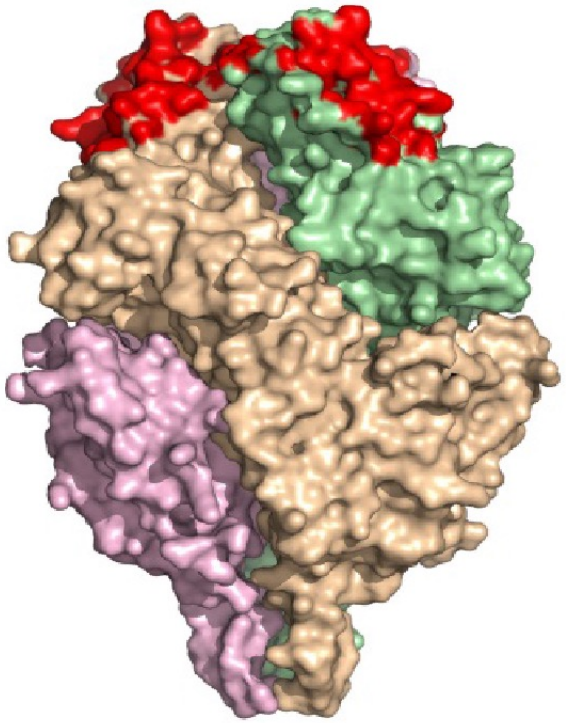


Stabilized, soluble trimer crystal structure resolved in detail

Image courtesy of M Pancera, J Stuckey, PD Kwong.

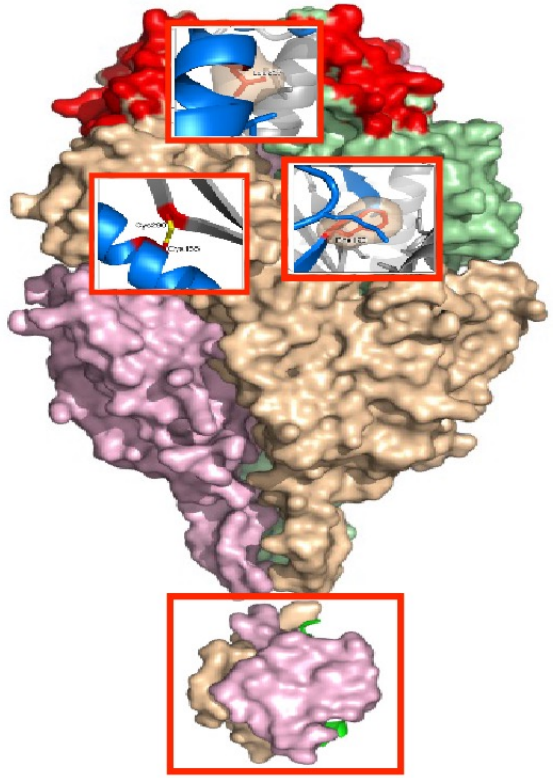
Pre-Fusion F Protein Stabilized Using Structure-Based Vaccine Design

Pre-Fusion F Protein



Stabilization

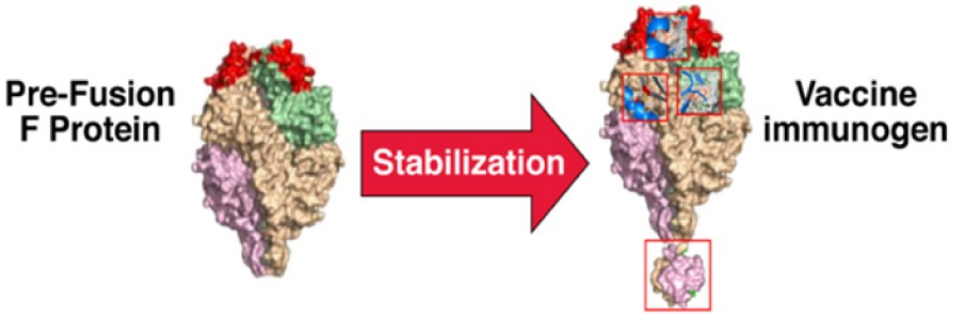
Vaccine immunogen



Source: McLellan JS, Chen M, et al. *Science* 342(6158), 2013.

Structure-Based RSV Vaccine Shows Promise in Phase 1 Trial – "Precision Vaccinology"

- RSV fusion glycoprotein stabilized in prefusion conformation (DS-Cav1) used as immunogen



A Proof of Concept for Structure-Based Vaccine Design Targeting RSV in Humans

MC Crank, BS Graham et al.,
for the VRC 317 Study Team

- 1 dose of DS-Cav1 induced large increases in RSV-neutralizing antibodies that were sustained for several months

Structure-based Design of MERS Vaccine

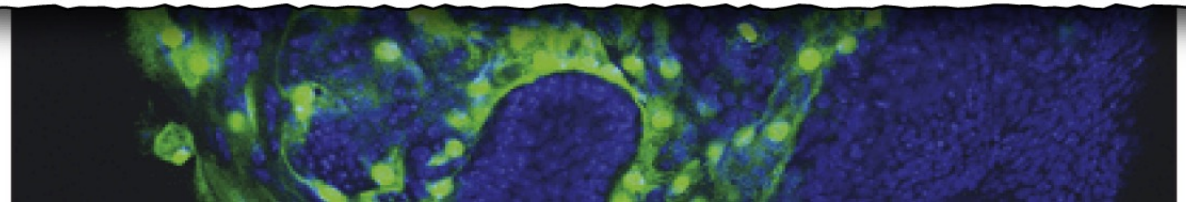
August 29, 2017

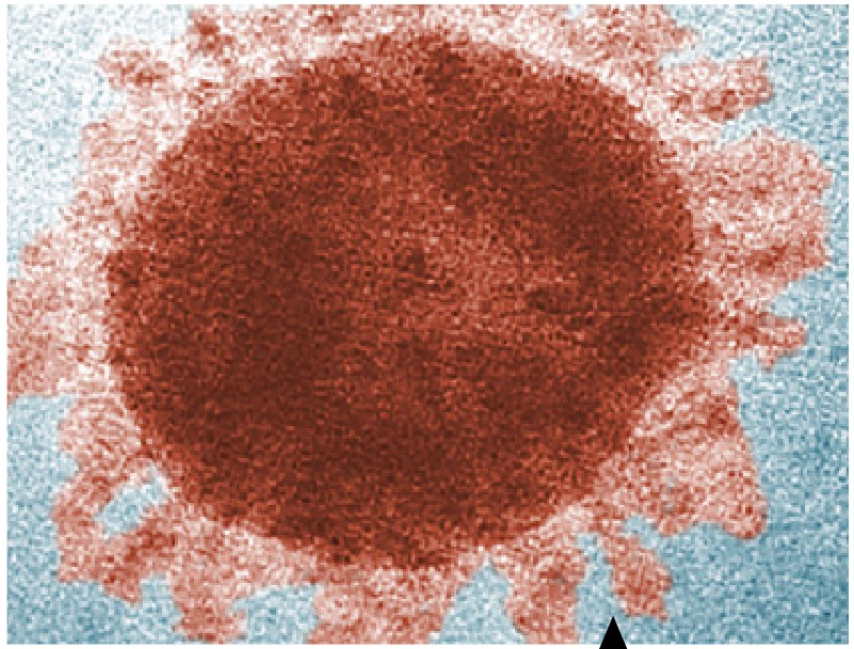
PNAS

Proceedings of the National Academy of Sciences of the United States of America

Immunogenicity and Structures of a Rationally Designed Prefusion MERS-CoV Spike Antigen

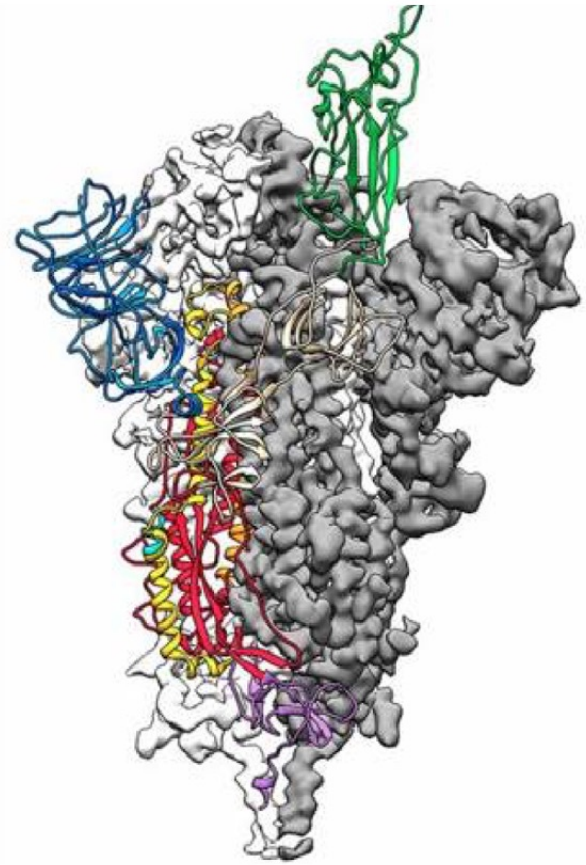
Jesper Pallesen, Nianshuang Wang, Kizzmekia S Corbett, Daniel Wrapp, Robert N Kirchdoerfer, Hannah L Turner, Christopher A Cottrell, Michelle M Becker, Lingshu Wang, Wei Shi, Wing-Pui Kong, Erica L Andres, Arminja N Kettenbach, Mark R Denison, James D Chappell, Barney S Graham, Andrew B Ward, Jason S McLellan



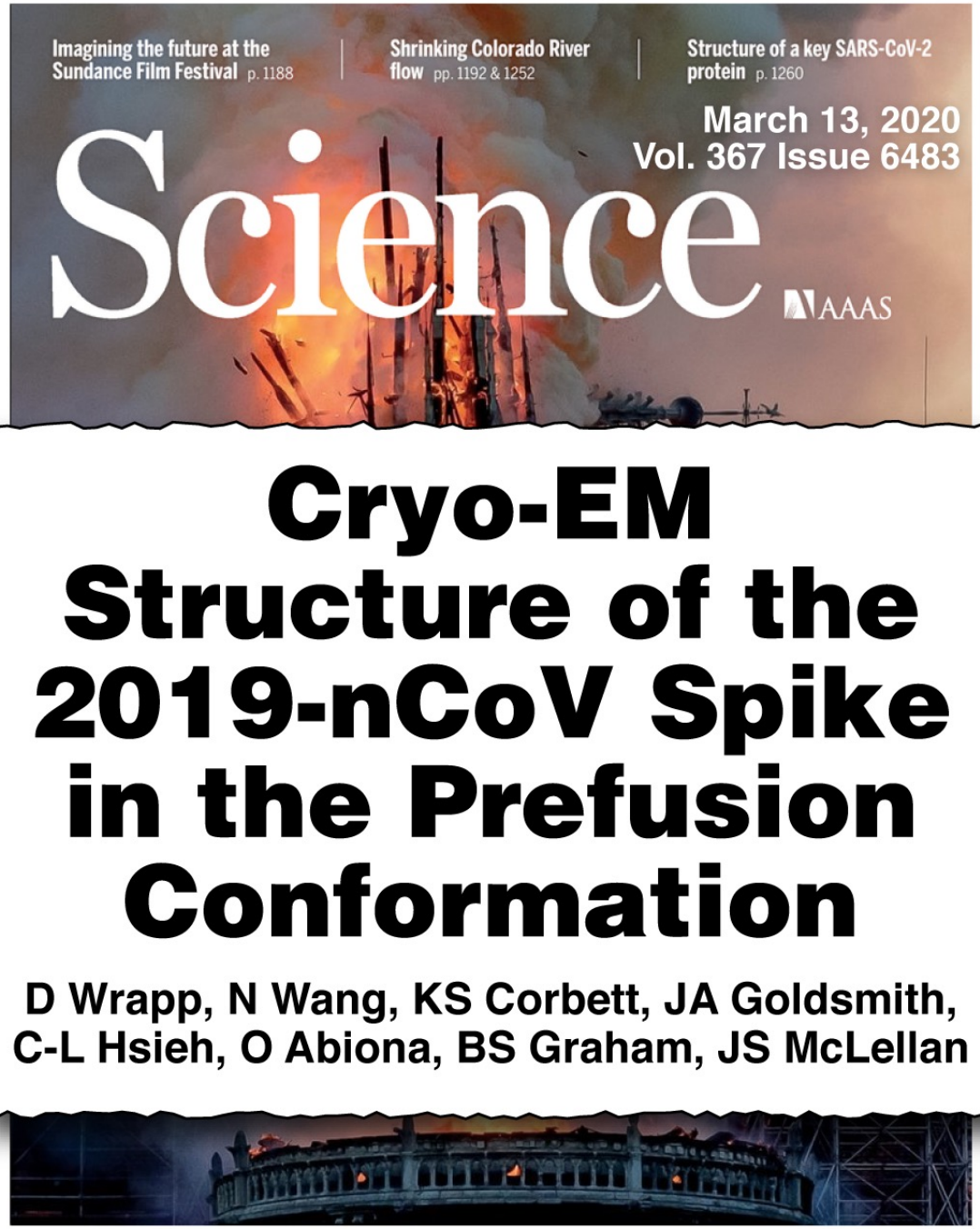


SARS-CoV-2
Spike protein
Pre-fusion
form
(Unstable)

Mutations

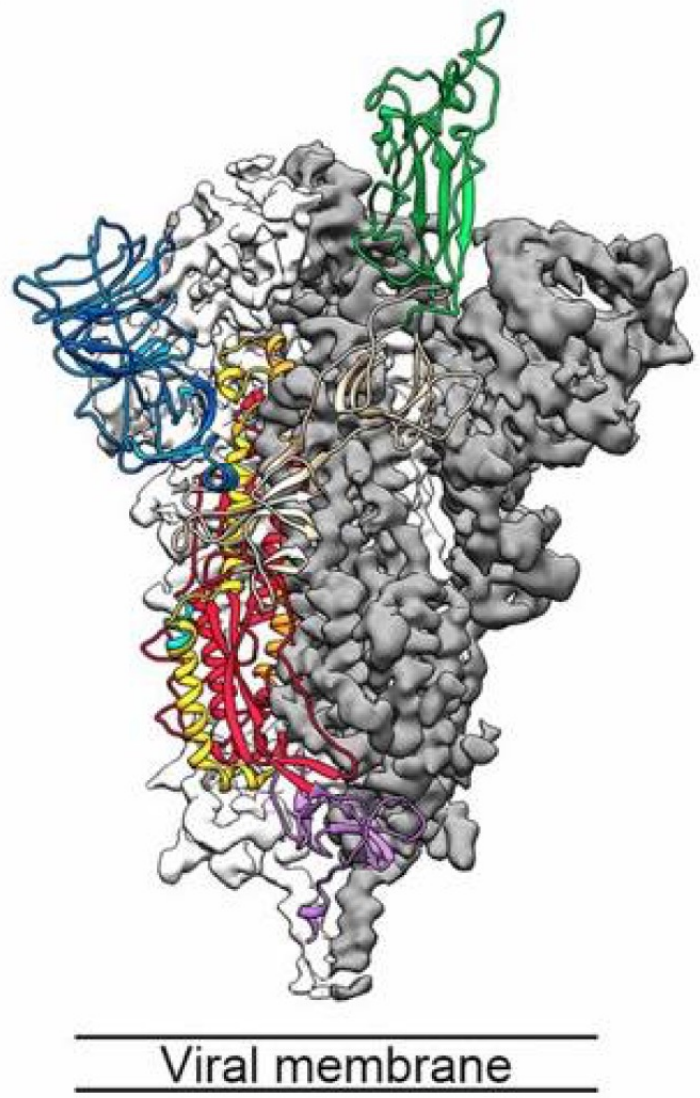


SARS-CoV-2
Spike protein
Pre-fusion
form
(Stable)

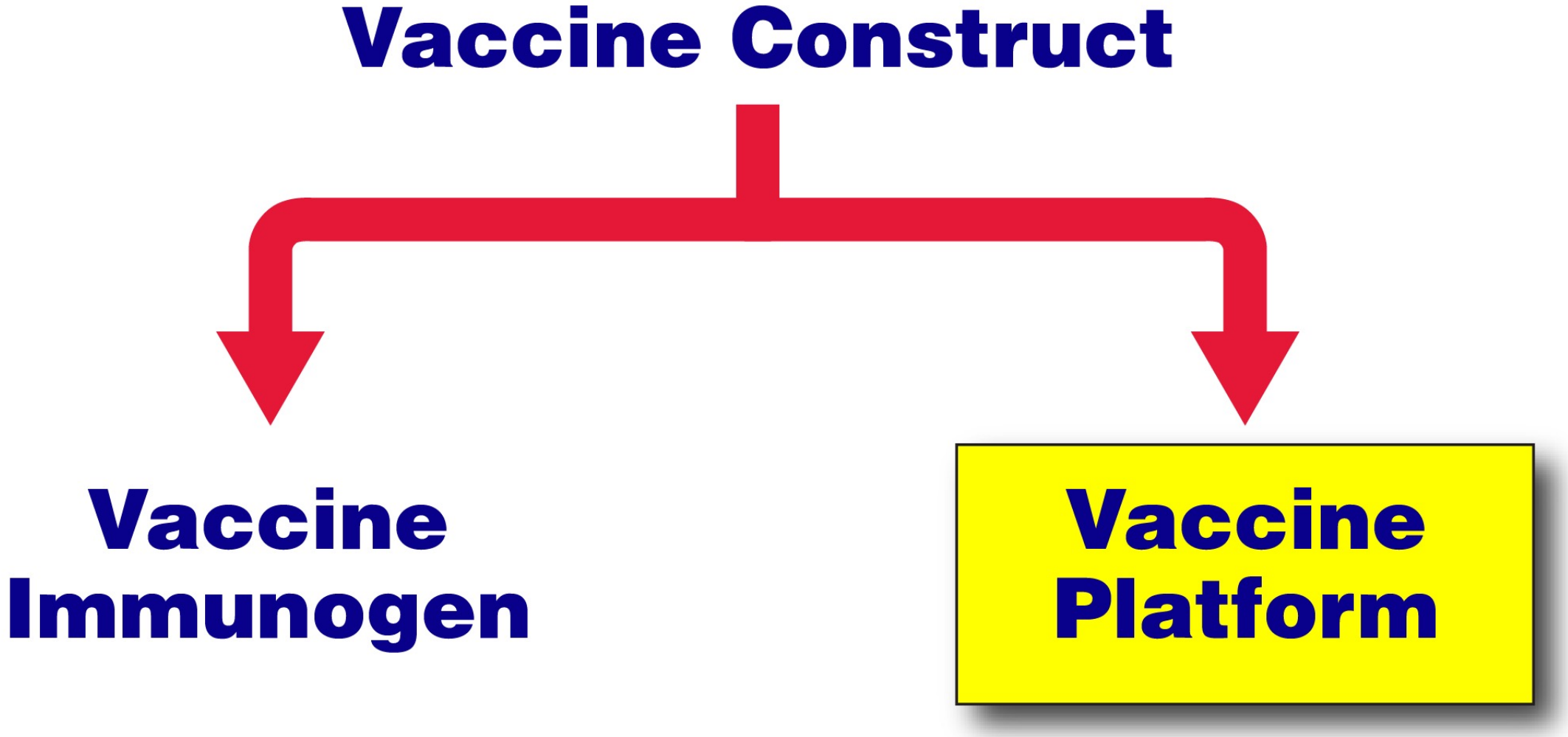


Cryo-EM Structure of the 2019-nCoV Spike in the Prefusion Conformation

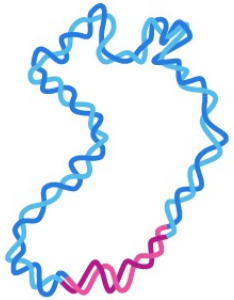
D Wrapp, N Wang, KS Corbett, JA Goldsmith, C-L Hsieh, O Abiona, BS Graham, JS McLellan



Atomic-level structure of SARS-CoV-2 spike protein. Receptor binding domain is colored green.

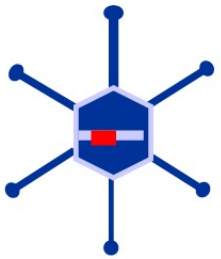

Vaccine Construct
Vaccine Immunogen
Vaccine Platform

Vaccine Platform Technologies



Genetic immunization (DNA and RNA vaccines)

SARS, MERS, West Nile, Zika, RSV

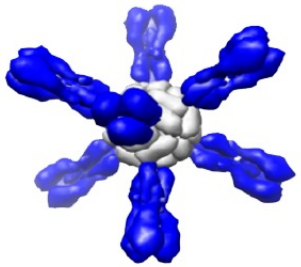


Viral vector (e.g., VSV, adenovirus)

Ebola, Marburg, Zika

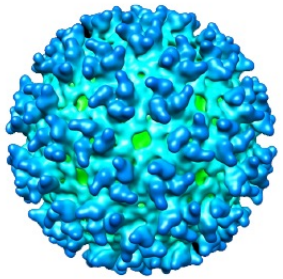
Recombinant protein

Influenza, RSV



Nanoparticles (viral protein on particle)

Influenza, Malaria, RSV



Virus-like particle (VLP) (no RNA or DNA; non-infectious)

Chikungunya, Zika, WEVEE

Adjuvants (e.g., AS01, MF59)

Selected Examples

Immunity
August 1, 2005

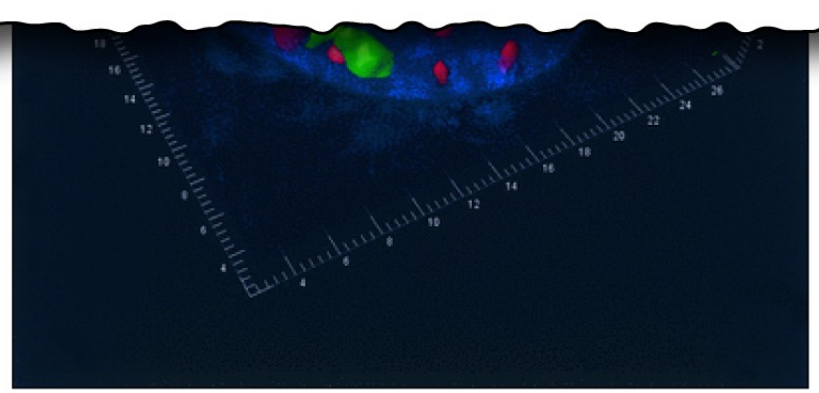
Suppression of RNA Recognition by Toll-like Receptors: The Impact of Nucleoside Modification and the Evolutionary Origin of RNA

K Karikó, D Weissman et al.

- Showed how to modify mRNA without triggering key inflammatory pathways, overcoming a key hurdle and paving the way for current vaccines

Comparative Seroprevalence and Immunogenicity of Six Rare Serotype Recombinant Adenovirus Vaccine Vectors from Subgroups B and D

P Abbink, DH Barouch et al.



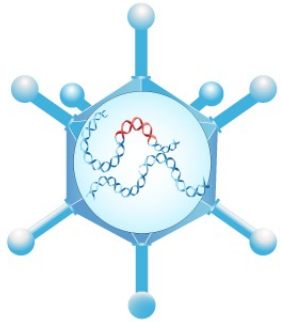
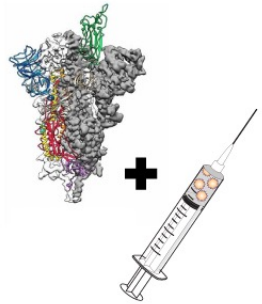
Journal of Virology

AMERICAN SOCIETY FOR MICROBIOLOGY

May 2007, Volume 81 Issue 9

- rAd26 vectors proved the most immunogenic among the rare serotype rAd vectors studied, with promise for vaccine development

Selected COVID-19 Vaccines

Platform		Developer	Status
Nucleic Acid (mRNA)		moderna	EUA
		BIONTECH Pfizer	EUA
Adenovirus Vector		Johnson & Johnson	EUA
		AstraZeneca	EUA TBD
Recombinant Protein and Adjuvant		gsk SANOFI	Phase 3 clinical trial launched May 2021
		NOVAVAX Creating Tomorrow's Vaccines Today	EUA TBD

Science's Breakthrough of the Year 2020: COVID-19 Vaccines

COVID-19 Vaccines are:

- Efficacious in clinical trials
- Effective in real-world settings
- Safe

COVID-19 Vaccines are:

- Efficacious in clinical trials
- Effective in real-world settings
- Safe

Pfizer/BioNTech Vaccine

The New England Journal of Medicine
Established in 1812 as THE NEW ENGLAND JOURNAL OF MEDICINE AND SURGERY
Published online December 10, 2020

Safety and Efficacy of the BNT162b2 mRNA COVID-19 Vaccine

FP Polack et al. for the
C4591001 Clinical Trial Group

Efficacy: 95%

Moderna Vaccine

The New England Journal of Medicine
Established in 1812 as THE NEW ENGLAND JOURNAL OF MEDICINE AND SURGERY
Published online December 30, 2020

Efficacy and Safety of the mRNA-1273 SARS-CoV-2 Vaccine

LR Baden et al. for the
COVE Study Group

Efficacy: 94.1%

Johnson & Johnson (Janssen) Vaccine

The New England Journal of Medicine

Established in 1812 as THE NEW ENGLAND JOURNAL OF MEDICINE AND SURGERY

Published online April 21, 2021

Safety and Efficacy of Single-Dose Ad26.COV2.S Vaccine against COVID-19

J Sadoff et al. for the ENSEMBLE Study Group

- 66% efficacy overall vs. moderate-to-severe COVID-19
  - 72% in United States
  - 68% in Brazil
  - 64% in South Africa
- 85% efficacy vs. severe disease across all regions studied

COVID-19 Vaccines are:

- Efficacious in clinical trials
- Effective in real-world settings
- Safe

“Real World” Vaccine Effectiveness Studies

The New England Journal of Medicine
Established in 1812 as THE NEW ENGLAND JOURNAL OF MEDICINE AND SURGERY
Published online March 23, 2021

Early Evidence of the Effect of SARS-CoV-2 Vaccine at One Medical Center

W Daniel, DK Podolsky et al.

- 23,234 employees of University of Texas Southwestern Medical Center, Dallas, TX; vaccination program initiated 12/15/2020
- 0.05% infection rate among fully vaccinated employees

CDC Centers for Disease Control and Prevention
CDC 24/7: Saving Lives, Protecting People™
April 2, 2021
Morbidity and Mortality Weekly Report (*MMWR*) Volume 70, Number 13

Interim Estimates of Vaccine Effectiveness of BNT162b2 and mRNA-1273 COVID-19 Vaccines in Preventing SARS-CoV-2 Infection Among Health Care Personnel, First Responders, and Other Essential and Frontline Workers — Eight U.S. Locations, December 2020–March 2021

- Prospective study; n=3,950
- mRNA vaccine effectiveness of full immunization (≥14 days after second dose) was 90% against SARS-CoV-2 infections regardless of symptom status; 80% after one dose
- 3 PCR-confirmed infections occurred during 78,902 person-days with full immunization (0.04/1,000 person-days)

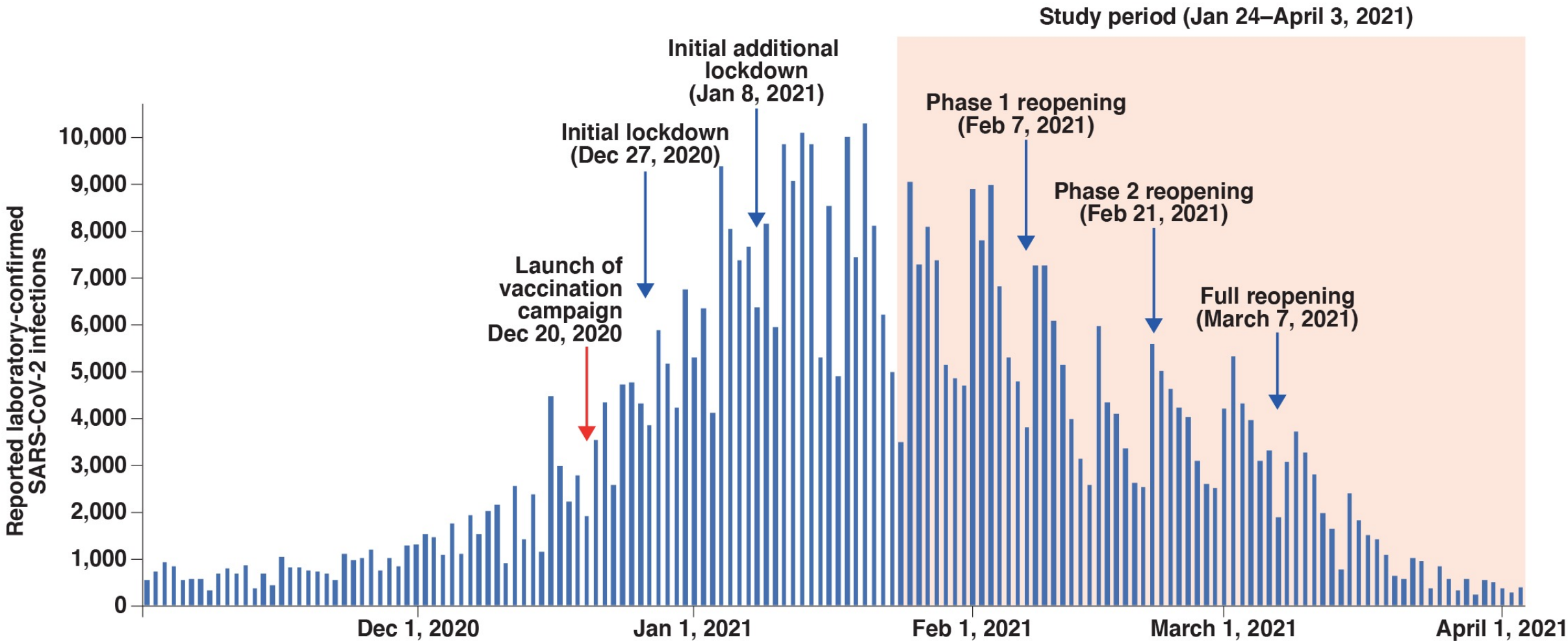
THE LANCET

published online May 5, 2021

Impact and Effectiveness of mRNA BNT162b2 Vaccine Against SARS-CoV-2 Infections and COVID-19 Cases, Hospitalisations, and Deaths Following a Nationwide Vaccination Campaign in Israel: An Observational Study Using National Surveillance Data

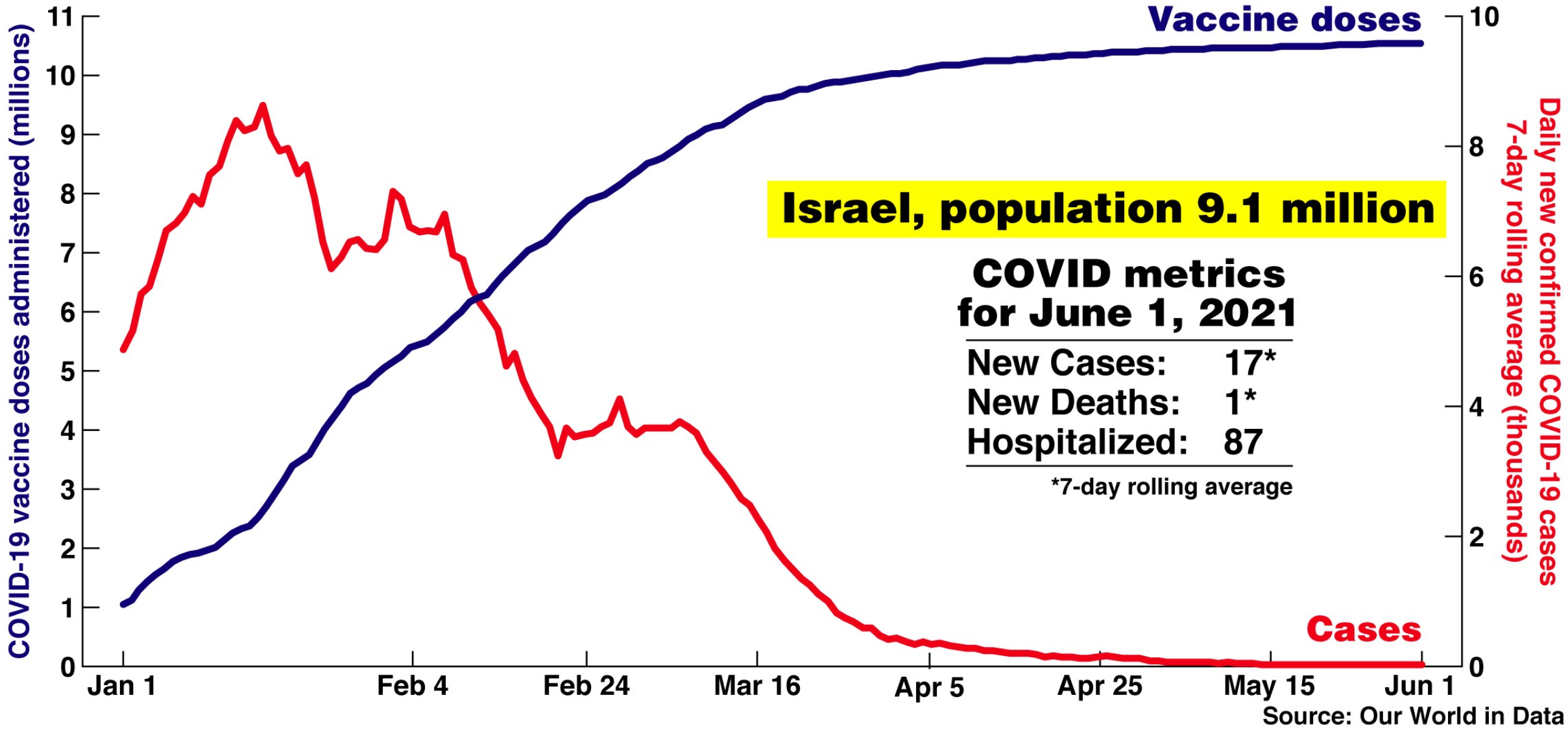
EJ Haas, S Alroy-Preis et al.

Daily Laboratory-Confirmed SARS-CoV-2 Infections in Israel – Nov. 1, 2020 to April 3, 2021



Source: EH Haas et al. *Lancet*, 5/5/2021.

Effect of Robust COVID-19 Vaccination Program in Israel



Source: Our World in Data

Estimated Effectiveness of 2 Doses of Pfizer/BioNTech COVID-19 Vaccine Against 6 Outcomes, Israel

- All ages, 201.9 million person-years total
- B.1.1.7 variant accounted for ~95% of SARS-CoV-2 infections

Estimated adjusted effectiveness, ≥7 days after the second dose, Jan 24 to April 3, 2021

SARS-CoV-2 infection	95.3%
Asymptomatic SARS-CoV-2 infection	91.5
Symptomatic COVID-19	97.0
COVID-19-related hospitalization	97.2
Severe or critical COVID-19-related hospitalization	97.5
COVID-19-related death	96.7

Source: EJ Haas et al. *Lancet*, 5/5/2021.

Estimated Effectiveness of 2 Doses of Pfizer/BioNTech COVID-19 Vaccine Against SARS-CoV-2 Infection, by Age Group, Israel

Estimated adjusted effectiveness, ≥7 days after the second dose, Jan 24 to April 3, 2021

Age Group	VE vs. SARS-CoV-2 infection
All ages	95.3%
Age 16-44 years	96.1
Age 45-64 years	94.9
Age ≥65 years	94.8
Age ≥75 years	95.1
Age ≥85 years	94.1

Source: EJ Haas et al. *Lancet*, 5/5/2021.

Centers for Disease Control and Prevention
CDC 24/7: Saving Lives, Protecting People™
May 14, 2021

Morbidity and Mortality Weekly Report (*MMWR*) *Early Release*

Interim Estimates of Vaccine Effectiveness of Pfizer-BioNTech and Moderna COVID-19 Vaccines Among Health Care Personnel — 33 U.S. Sites, January–March 2021

- **Test-negative design case-control study; 623 case-patients and 1,220 controls in 25 states**
- **Adjusted vaccine effectiveness (VE) of 2 doses of Pfizer-BioNTech or Moderna COVID-19 (measured ≥7 days after the second dose): 94% against symptomatic COVID-19**
- **VE after 1 dose: 82%**

Powered by SSRN

Preprints with THE LANCET

Published online May 10, 2021

Real-World Effectiveness of Ad26.COV2.S Adenoviral Vector Vaccine for COVID-19

J Corchado-Garcia et al.

- Multi-state Mayo Clinic health system (MN, AZ, FL, WI, IA)
- After at least 2 weeks of follow-up, 3 of 1,779 people vaccinated with Johnson & Johnson vaccine tested positive for SARS-CoV-2 compared to 128 of 17,744 unvaccinated individuals
- Vaccine effectiveness: 76.7%

COVID-19 Vaccines are:

- Efficacious in clinical trials
- Effective in real-world settings
- Safe

Ensuring COVID-19 Vaccine Safety in the U.S.

- Clinical trials
- Expanded safety monitoring systems
  - CDC: V-safe
  - CDC: National Healthcare Safety Network (NHSN)
  - FDA: Other large insurer/payer databases
- Other safety monitoring systems
  - CDC and FDA: Vaccine Adverse Event Reporting System (VAERS)
  - CDC: Vaccine Safety Datalink (VSD)
  - CDC: Clinical Immunization Safety Assessment (CISA) Project
  - FDA and the Centers for Medicare and Medicaid Services: Medicare data
  - FDA: Biologics Effectiveness and Safety System (BEST)
  - FDA: Sentinel Initiative
  - DoD, VA systems

Source: https://www.cdc.gov/coronavirus/2019-ncov/vaccines/reporting-systems.html

Impact of Viral Variants on Vaccine Effectiveness

Selected SARS-CoV-2 Variants

B.1.1.7
originally United Kingdom

B.1.351
originally South Africa

P.1
originally Brazil

B.1.429/B.1.427
originally California

B.1.526
originally New York

B.1.617
originally India

The New England Journal of Medicine

Established in 1812 as THE NEW ENGLAND JOURNAL OF MEDICINE AND SURGERY

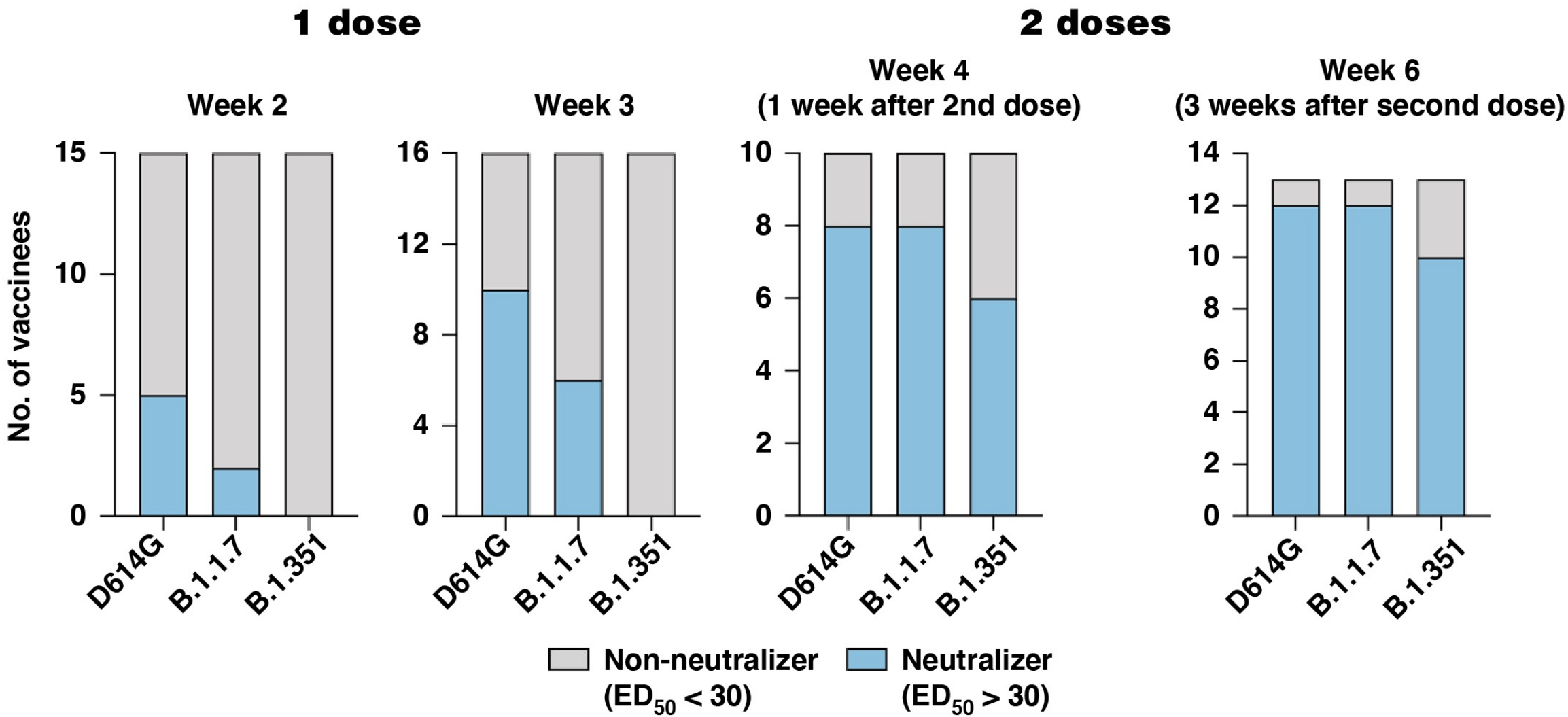
Published online May 5, 2021

Effectiveness of the BNT162b2 COVID-19 Vaccine against the B.1.1.7 and B.1.351 Variants

LJ Abu-Raddad et al. for the National Study Group for COVID-19 Vaccination

- Mass vaccination campaign in Qatar; total n=385,853
- **Vaccine effectiveness against any documented infection**
  - **B.1.1.7** -- 89.5% after 2 doses, 29.5% after 1 dose
  - **B.1.351** -- 75.0% after 2 doses, 16.9% after 1 dose
- **Vaccine effectiveness against severe, critical, or fatal disease**
  - **B.1.1.7** -- 100% after 2 doses, 54.1% after 1 dose
  - **B.1.351** -- 100% after 2 doses, 0% after 1 dose

Improved Neutralization of SARS-CoV-2 Variants After 2nd Pfizer Vaccine Dose



Source: D Planas et al. *Nature Med*, March 26, 2021.

The New England Journal of Medicine

Established in 1812 as THE NEW ENGLAND JOURNAL OF MEDICINE AND SURGERY

Published online May 12, 2021

BNT162b2-Elicited Neutralization against New SARS-CoV-2 Spike Variants

Y Liu, P-Y Shi et al.

- **The newly emerged B.1.526, B.1.429, and B.1.1.7+E484K variants remain susceptible to neutralizing antibodies**
- **The E484K mutation (also found in the B.1.351 and B.1.526 lineages) caused little compromise to neutralization**

May 16, 2021

Cold Spring Harbor Laboratory

bioRxiv

THE PREPRINT SERVER FOR BIOLOGY

Durability of mRNA-1273-Induced Antibodies Against SARS-CoV-2 Variants

A Pegu, NA Doria-Rose et al.

- **Most individuals vaccinated with mRNA-1273 (Moderna vaccine), including older individuals, maintained binding and functional antibodies against SARS-CoV-2 variants B.1.1.7, B.1.351, P.1, B.1.429, and B.1.526 antibodies for >6 months.**
- **“While the correlates of vaccine-induced protection are not yet known, our data are encouraging for the use of this vaccine in the face of viral variation.”**

Update on the B.1.617 Variant

- **The modest neutralization resistance of B.1.617.1 variant to vaccine-elicited antibodies suggests that current vaccines will be protective**

- **Selected references:**

Cold Spring Harbor Laboratory bioRxiv THE PREPRINT SERVER FOR BIOLOGY

May 8, 2021

SARS-CoV-2 B.1.617 Emergence and Sensitivity to Vaccine-Elicited Antibodies

I Ferreira, RK Gupta et al.

Cold Spring Harbor Laboratory bioRxiv THE PREPRINT SERVER FOR BIOLOGY

May 9, 2021

Infection and Vaccine-Induced Neutralizing Antibody Responses to the SARS-CoV-2 B.1.617.1 Variant

V Edara, MS Suthar et al.

Cold Spring Harbor Laboratory bioRxiv THE PREPRINT SERVER FOR BIOLOGY

May 12, 2021

Neutralization Potential of Covishield Vaccinated Individuals Against B.1.617.1

PD Yadav, B Bhargava et al.

Cold Spring Harbor Laboratory bioRxiv THE PREPRINT SERVER FOR BIOLOGY

May 14, 2021

The Spike Proteins of SARS-CoV-2 B.1.617 and B.1.618 Variants Identified in India Provide Partial Resistance to Vaccine-Elicited and Therapeutic Monoclonal Antibodies

T Tada, NR Landau et al.

Public Health England

Press Release

May 22, 2021

Vaccines Highly Effective Against B.1.617.2 Variant after 2 Doses

From April 4 to to May 16, 2021,

- 2 weeks after the second dose, Pfizer-BioNTech vaccine was 88% effective against symptomatic disease from B.1.617.2 variant and 93% effective against B.1.1.7 variant
- 2 doses of AstraZeneca vaccine were 60% effective against B.1.617.2 and 66% effective against B.1.1.7
- 3 weeks after first dose, both vaccines were 33% effective against symptomatic disease from B.1.617.2 and ~50% effective against B.1.1.7

The Race is On